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QUARTERLY
MEDICAL REVIEW

Vol. 35 No. 1 **January 1984**

HYPERTENSION

P. S. Shankar*

'Hypertension is a qualitative deviation from the normal, and there is no dividing line between normal and high blood pressure'. When the blood pressure at different age groups in a large healthy population is plotted, it does not demonstrate two distinct groups as normotensive and hypertensive[1].

The measurement of arterial blood pressure was made possible by the development of a prototype of the modern sphygmomanometer in 1896, but it was incorporated in routine physical examination only in the middle of the present century. Hypertension is noted in 10-15% of population in India and has become a common health problem[2]. **Nearly 50% of the individuals with hypertension exhibit hypertensive heart disease.** However many of them go undected and untreated. The timely recognition and proper treatment reduces the overall morbidity and mortality.

Arterial blood pressure gradually increases with age. In adults, a blood pressure of 140/90 mm Hg is often considered the upper limit of normal. According to the recommendations of WHO, the blood pressure of 160/95 mm Hg or higher should be considered hypertension[3].

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Systolic hypertension is caused from an increased cardiac output or arterial rigidity. Arterial rigidity usually occurs in elderly individuals and is a manifestation of atherosclerosis. Diastolic hypertension develops from increased vascular resistance to the blood flow at the level of arterioles. Generally systolic and diastolic hypertension occur together. Arterial hypertension is labelled symptomatic or secondary when its cause has been identified, and essential (idiopathic) when its cause remains undetermined.

For quite some time, arterial hypertension may exist without any symptoms or signs of disturbances in structure and function of organs. It may come to light only when the arterial blood pressure is recorded. Long term hypertension leads to characteristic changes in the vessels of retina, brain, heart and kidneys (target organs). Arterial hypertension may be labile or sustained. Labile hypertension refers to periodic elevation of blood pressure above the normal range. Sustained hypertension may get accelerated (retinal haemorrhages and exudates) or it may enter into malignant phase (papilloedema and renal damage). Malignant hypertension is characteristically associated with fibrinoid and necrotising arteriolitis.

AETIOLOGY & PATHOPHYSIOLOGY

Arterial blood pressure is the product of cardiac output and peripheral vascular resistance. Cardiac output is dependent on myocardial contractile state, length of cardiac muscle at the onset of contraction (preload), tension which the muscle has to develop during contraction (afterload) and heart rate. Peripheral vascular resistance is dependent on the ratio of lumen dimension to wall thickness, and on the neurohumoral influence particularly noradrenalin, angiotensin II (vasoconstrictors), and acetylcholine, kinins and prostaglandins (vasodilators) that act on vascular smooth muscle.

Different mechanisms affect the cardiac output and peripheral vascular resistance and increase them singly or together to bring about an elevation of blood pressure. Though a variety of conditions are responsible for hypertension (table I) in nearly 90% of patients, the aetiology remains undetermined.

ESSENTIAL HYPERTENSION

'Blood pressure is a measurable end product of an exceedingly complex series of factors including those which control blood vessel calibre and responsiveness, those which control fluid volume within and outside the vascular bed, and those which control cardiac output[4]. These factors are closely related with each other. It is difficult to find out a single cause for essential hypertension and a mosaic of many interacting factors such as cardiac output, vascular calibre, elasticity and reactivity, blood volume and viscosity, neural and chemical factors are likely to bring about hypertension[5].

Among neural and chemical factors, the altered function of central nervous system and sympathetic nervous system, renin-angiotensin-aldosterone system and deficiency of renal vasodilator substances are important.

Table I : Causes of Hypertension

1. Essential hypertension
2. Secondary hypertension
   - I) with systolic and diastolic hypertension
     - i) Renal:
       - a) Parenchymal: acute and chronic glomerulonephritis, chronic pyelonephritis, polycystic kidney, connective tissue diseases (Progressive systemic clerosis, systemic lupus erythematosus), diabetic nephropathy, hydronephrosis, hypernephroma, juxtaglomerular (JG) cell tumour, Wilm's tumour
       - b) Renovascular: atherosclerotic, thrombotic or embolic obstruction, fibromuscular hyperplasia, aneurysm, polyarteritis, hypoplasia
       - c) Renal compression: renal haematoma, perinephritis, fibrous constriction, obstructive uropathy
     - ii) Endocrine :
       - a) Adrenal: hyperaldosteronism, Cushing's syndrome, congenital or hereditary adrenogenital syndromes (17 alpha hydroxylase and 11 beta hydroxylase defects), pheochromocytoma
       - b) Thyroid and Parathyroid: hypothyroidism, hyperparathyroidism
       - c) Pituitary: acromegaly
     - iii) Neurogenic: raised intracranial tension, bulbar poliomyelitis, encephalitis, polyneuritis, acute porphyria, lead poisoning, brain tumours, ganglioneuroma, cord transection
     - iv) Toxaemia of pregnancy: pre-eclampsia, eclampsia
     - v) Coarctation of the aorta: thoracic or abdominal
     - vi) Drug - or diet-induced:
       - a) drug: oral contraceptives, steroids, monoamine oxidase inhibitors, sympathomimetic amines, amphetamines,
       - b) diet: liquorice ingestion, tyramine - rich foods

II) with systolic hypertension
   - i) Increased left ventricular stroke volume: complete heart block, aortic incompetence, patent ductus arteriosus, arteriovenous fistula, severe anaemia, beri beri
   - ii) Reduced aortic distensibility: aortic atherosclerosis, coarctation of aorta

Borst and Borst de Geus have shown that the initiation and development of essential hypertension occurs on a primary basic defect of increased retention of salt and water by the kidneys[6]. A defective transport of sodium at the renal tubule leads to renal sodium retention. It results in an expanded plasma and extracellular fluid volume. It raises central venous pressure and preload resulting in an increased cardiac output. However the autoregulatory mechanisms prevent increased tissue perfusion by increasing the local vascular resistance at many vascular beds. The raised blood pressure acts as negative feedback by increasing cardiac afterload thus depressing the stroke volume and cardiac output.

However, in essential hypertension, this relation is deranged and sodium elimination is not increased in presence of high blood pressure. Body tries to reset the renal perfusion pressure—natriuresis control mechanism and it brings back blood volume and cardiac output to normal. However the elevated blood pressure remains persistently at a high level in presence of increased peripheral vascular resistance. The increased peripheral vascular resistance can occur from the effect of factors that produce vasoconstricion or from the reduction in the factors producing vasodilatation or from an alteration in the arterial smooth muscle reacting to vasoconstrictor stimuli.

Heredity and Salt Intake :

Heredity plays a role in the production of hypertension. Abnormal renal handling of sodium can be inherited as a specific genetic defect in some individuals. A high intake of salt in individuals with genetic predispostion is likely to result in renal retention of salt and in turn of water, and expansion of plasma volume.

The frequency of hypertension is closely related with the level of dietary sodium intake especially in patients with reduced renal function[7]. Epidemiologic studies have shown that there is an increased incidence of hypertension in populations with very high salt consumption[8]. On the other hand, the incidence of hypertension is much less in those communities taking little salt[9]. In addition, salt raises the blood pressure by increasing peripheral vascular resistance. More sodium is retained in arteries of hypertensives. There is also an associated high level of ionized calcium in the arterial smooth muscle cell, thus contributing to an increased vascular resistance.

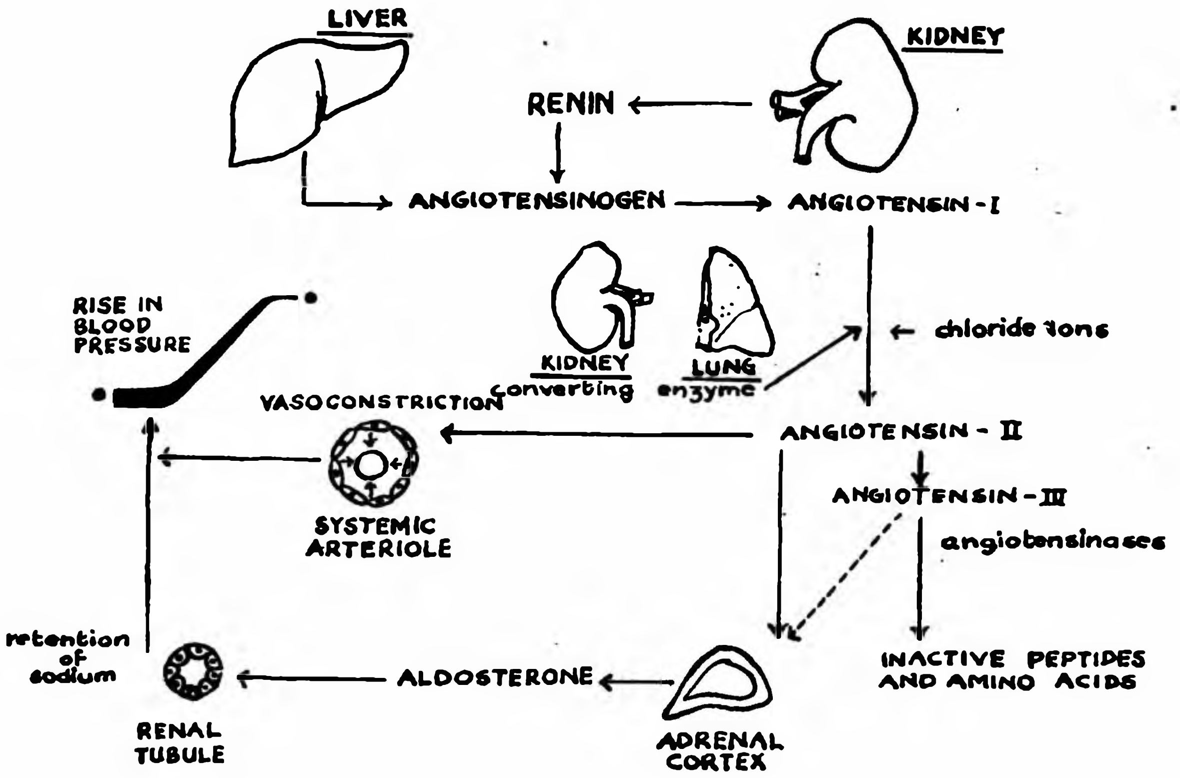
Though the plasma volume and cardiac output initiate hypertension, it becomes sustained by an increased peripheral vascular resistance. The adaptive changes in the vessels in the form of its constriction and inter-thickening of the vessel walls maintain raised blood pressure. The vessels exhibit an increased sensitivity to one or more vasopressor agents and further raise increased peripheral resistance.

Renin-Angiotensin-Aldosterone System :

Since the demonstration by Goldblatt in 1934 that interference with the arterial blood supply to one or both kidneys results in hypertension, attempts have been made to know its mechanism and evidences have pointed out that the mechanism is humoral, and the kidney has an endocrine function[10]. It is mediated by the enzyme renin, which plays an important role in the maintenance of blood pressure[11].

Renin is a proteolytic enzyme. It is stored primarily in the kidney in its juxtaglomerular cells of the renal cortex[12]. It is released from the juxtaglomerular apparatus into afferent glomerular arterioles in response to the factors reducing the arterial blood pressure and renal blood flow[13], and also markedly reduced dietary sodium[14].

Renin cleaves leucine and leucine bond of the alpha$_2$ globulin substrate (angiotensinogen) released from the liver to produce angiotensin decapeptide, angiotensin I. The converting enzyme, located in vascular beds of the lungs, kidney, testes, and brain in presence of chloride ions, removes two terminal amino acids (leucine and histidine) of biologically inactive angiotensin I to produce angiotensin octapeptide, angiotensin II. Angiotensin II is a highly powerful pressor hormone. It causes marked arteriolar vasoconstriction acting directly on the systemic arterioles and indirectly through hypothalamic adrenergic activity to raise the blood pressure[14]. At the



RENIN - ANGIOTENSIN - ALDOSTERONE - CHAIN same time it acts as a potent stimulus for synthesis of aldosterone in the adrenal cortex which in turn acts on the renal tubules to cause sodium and fluid retention, and expansion of extracellular fluid volume. Angiotensin II is converted to angiotensin heptapeptide, angiotensin III,by the action of aminopeptidase. It has been shown that angiotensin III is more active than angiotensin II in stimulating aldosterone release. It gets further degraded into inactive fragments[15].

When the pressure and the blood flow are raised as a result of increased level of renin, negative feedback signals stop release of renin by acting on the intrarenal baroreceptors in the afferent renal arterioles and on sodium load receptors in the macula densa of the distal tubules (fig. 1).

Normally renal tissue contains a specific amount of renin and the material also circulates in the plasma. Plasma renin activity (PRA) is a measure of 'active' renin and plasma renin concentration. Renin-angiotensin-aldosterone is a potent interrelated pressor mechanism and their level may be very high in some hypertensives to bring about increased vascular reactivity. The secretion of renin and aldosterone vary in response to variations in salt intake. Their secretion increases in presence of sodium depletion and gets diminished in presence of high levels of sodium. Hence PRA value has to be assessed against sodium balance. PRA value is related to 24-hour urinary sodium excretion. PRA on a normal diet is 1.1 ± 0.8 ng/ml/h(supine) and 1.9 ± 1.7 ng/ml/h(upright)[16].

Hypertension has been divided into three types on the basis of plasma renin activity. There may be low plasma renin activity (volume overload), or normal or high plasma renin activity (vasoconstrictor type)[17] (Table II)

Table II : Renin level and Hypertension

1. *Low renin hypertension :* low renin essential hypertension, primary hyperaldosteronism, 11-beta-hydroxylase deficiency, 17-alpha hydroxylase deficiency, ectopic ACTH secreting tumours, idiopathic deoxycorticosterone excess, 18-hydroxy corticosterone excess, 19-hydroxy-corticosterone excess, Liddle syndrome, adrenal carcinoma, mineralocorticoid or liquorice ingestion

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2. *Normal renin hypertension :* normal renin essential hypertension, renal parenchymal hypertension, pheochromocytoma, Cushing's syndrome
3. *High renin hypertension :* High renin essential hypertension, malignant hypertension, renal artery stenosis, renin-secreting kidney tumours, oral contraceptives, primary reninism (Robertson syndrome)

Low renin activity may be associated with normal or increased level of mineralocorticoids. In the former, essential hypertension is noted in 20-25% of cases and the patients belong to elderly age group. PRA decreases with age and it is probably due to decrease in renal mass or juxtaglomerular apparatus. There is reduced sympathetic activity and the renin responsiveness is low. These cases respond well to diuretics. An increased level of mineralocorticoids may be seen in less than 5% of patients with low PRA. The level of aldosterone or deoxycorticosterone (DOC) is markedly elevated. Hypertension in such cases responds to spironolactone and to adrenal inhibitor, aminoglutethimide.

High plasma renin activity may be seen in 5-10% cases of essential hypertension and is noted frequently in young persons. The condition is often associated with renal hypoperfusion, renal compression, glomerulonephritis, and hydronephrosis. The response to diuretics is poor. Beta-adrenergic blockers and sympatholytics such as methyldopa, clonidine and rauwolfia preparations reduce renin activity.

The individuals with high renin show more vasoconstriction and those with low renin exhibit volume expansion. However this distinction may not accurately reflect the haemodynamic abnormalities[18].

Renal Vasodilator Substances

A deficiency of renal vasodilator substances has been considered another important causative factor in essential hypertension.

Kallikrein-Kinin System : Kallikreins are endogenous enzymes that catalyse the formation of a most potent vasodilator substance, bradykinin, from high molecular weight kininogens[19]. It is evident from the earlier discussion that the transportation of sodium and water, and intrarenal circulation play an important role in the maintenance of normal blood pressure. Kallikrein is stored in the cells lining the distal convoluted tubules from the juxtaglomerular apparatus to the collecting tubules of the renal cortex. The kinins have an intra-renal effect and they produce renal vasodilatation. There is an enhanced excretion of sodium, potassium and water.

Renin-angiotensin system and kallikrein-kinin system are physiologically inter-related. There is a negative correlation between the level of plasma renin activity and blood kinin concentration. A fall in the level of renal kallikrein concentration causes hypertension. There is an inverse relationship between blood pressure and urinary excretion of kallikrein[20].

Prostaglandins : Prostaglandin A_2 (PGA_2) and prostaglandin E_2 (PGE_2) are produced in the renomedullary interstitial cells. They act in opposing ways, to bring down the blood pressure. PGA acts as circulating antihypertensive agent and PGE causes renal vasodilatation and an increased excretion of sodium, chloride, potassium and water.

There appears to be a local vasoregulatory role at the site of release of prostaglandins. A high sodium intake is associated with fall in plasma concentration of PGA_2 and low sodium intake causes an elevation of PGA_2 concentration in the plasma[21]. PGA acts on adrenal cortex stimulating aldosterone secretion and peripheral vasodilatation. Thus it nullifies the effect of sodium retention.

An impaired production of PGE_2 affects the intrarenal circulation and brings about hypertension. A decreased synthesis of prostaglandin leads to volume-expanded hypertension by increasing medullary sodium gradient and increased fluid retention. Neutral lipids present in the interstitial cells of renal medulla appear to act as precursors of prostaglandins and have a vasodilator effect.

Of the prostaglandins, prostacyclin (PGI_2) is the most powerful vasodilator and is formed from arachidonic acid in the renal vascular tree in the cortex. As it is not extracted by lungs, kidneys and liver, unlike PGE_2, it appears to be a powerful circulating hormone participating in renin release or acting as a vasodilator[22].

Sympathetic Nervous System

The function of sympathetic nervous system is altered in persons with essential hypertension. Sympathetic overactivity is suspected as the cause in some hypertensives. Mild or borderline hypertension may occur as a psychosomatic disturbance. Peripheral resistance is enhanced by alpha sympathetic activity. Beta sympathetic activity will increase plasma renin levels and the cardiac output[23].

Sympathetic overactivity is noted in presence of stimuli such as emotional stress, cold and exercise and there is an increased response in the heart rate, cardiac output, blood pressure, plasma catecholamine levels and renal renin release. At least in 30% of patients the increased peripheral vascular resistance is maintained by raised alpha adrenergic tone. There is close link between neural and non-neural, especially chemical,factors.

There is an exaggerated sympathetic response through angiotensin II in renal hypertension. Sympathetic stimulation results in release of renin by its direct action on juxtaglomerular apparatus. An increased sympathetic activity, as evident by high levels of plasma catecholamines, suggests that sympathetic activity is concerned in sustaining elevated blood pressure in essential hypertension[24].

SECONDARY HYPERTENSION

In nearly 10% of cases, hypertension develops secondary to an underlying disease and presents as renal hypertension, endocrine-type hypertension, vascular form of hypertension, neurogenic hypertension, and drug or diet-induced hypertension. It is necessary to recognise the underlying disorder as many of them are curable.

Renal Hypertension

Renal disorders produce hypertension either from a volume expansion due to deranged handling of sodium and water or from change in the arteriolar tone due to an alteration in renal secretion of vasoactive substances. Renal parenchymal diseases, renal compression and renovascular conditions are associated with hypertension.

Hypertension is noted in acute and chronic glomerulonephritis. Volume overload is responsible for hypertension in acute glomerulonephritis. The coexisting renal failure raises the blood pressure in chronic glomerulonephritis. Chronic pyelonephritis is a frequent cause of hypertension in young women. Hypertension develops from interference with intrarenal circulation or from renal failure. The renin level is normal.

Collagen diseases such as progressive systemic sclerosis and systemic lupus erythematosus are associated with hypertension. The impaired renal function due to intercapillary glomerulosclerosis in diabetic nephrosclerosis leads to the development of hypertension. The level of plasma renin activity is significantly low.

Renal tumours (JG cell tumour, nephroblastoma) noted in young individuals are associated with severe hypertension, marked hypokalaemia, increased production of aldosterone and increased peripheral renin activity unlike primary aldosteronism. These tumours are quite small and are recognised by selective renal angiography. The level of renal vein renin concentration is increased on the affected side. Wilm's tumour is associated with hypertension and hyperreninaemia. Hypernephroma produces large intrarenal masses and produces hypertension by interfering with renal circulation and stimulating renin release. Hypertension noted in polycystic kidney is not renin mediated and it is caused by pyelonephritis or from ischaemia of the kidneys resulting from mechanical compression of the renal arteries by cysts or from obstruction to the flow of urine in the upper urinary tract.

Renal artery lesions produced by atherosclerosis and fibromuscular dysplasia result in hypertension in one to two percent of patients. The great variety of the clinical features and the absence of pathognomonic signs make the diagnosis of renal vascular hypertension difficult. The atherosclerotic obstruction occurs in the proximal portion of the renal artery. It is common in elderly men. The fibrous dysplasia is often noted in women before the age of 30 years and it affects the middle and distal portions of the renal artery. Renovascular hypertension should be suspected if hypertension is severe or refractory to treatment or shows progressive increase in its severity.

Renal artery stenosis may be recognised by the presence of systolic bruit in the abdomen, hypokalaemia, polycythaemia and even ptotic kidney[25]. Intravenous pyelography examination shows the kidney on the affected side to be smaller than the unaffected side. There is a delay in the affected kidney getting contrasted and

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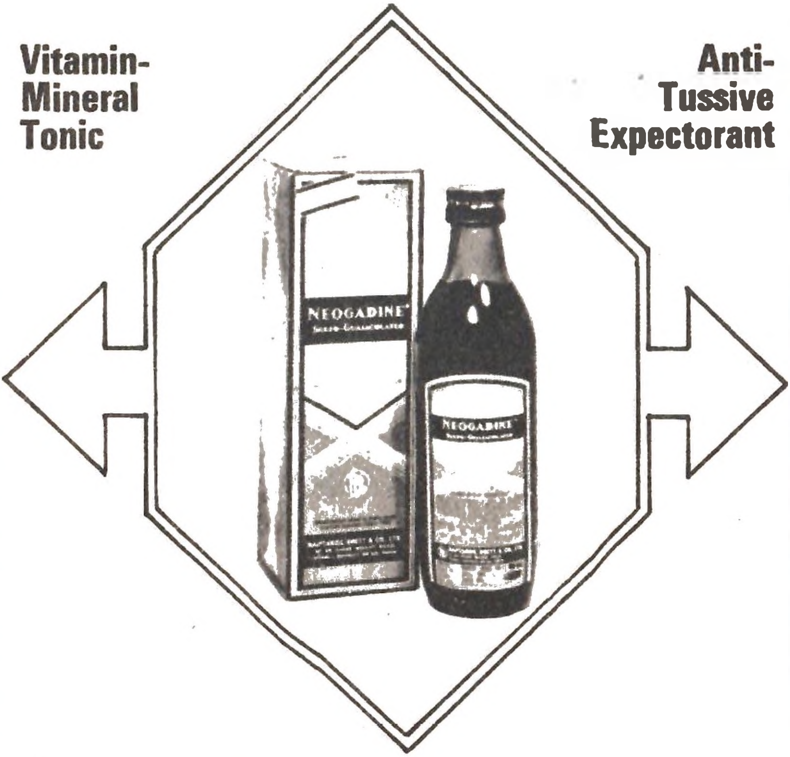

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freed of the contrast media. IVP may even demonstrate ptosis of the kidney and ureteral notching from collateral vessels to ischaemic kidney. Several constricted segments, each followed by a post-stenotic dilatation giving appearance of a string of beads, may be noted in the wall of the affected kidney in fibromuscular dysplasia.

Angiography and renal vein renin estimation are necessary to confirm the diagnosis. The level of renin may be at least 50 to 100% higher than that of the unaffected side[26]. Diuretics, vasodilators and captopril stimulate renin release and increase the difference between two sides. A rapid infusion of saralasin shows a reduction more than 10 mm Hg diastolic blood pressure when the hypertension is angiotensin dependent[27].

Renovascular hypertension responds to surgical treatment either by nephrectomy or corrective renovascular surgery. However mild hypertension can be managed by antihypertensive agents (betablockers and captopril). Transluminal renal angioplasty involves a technique of inflation of balloon portion of catheter under pressure which has been positioned in the stenotic part of the artery[27].

ENDOCRINE FORMS OF HYPERTENSION

Mineralocorticoid Excess Syndrome :

Primary Hyperaldosteronism : Aldosterone, an adrenocortical hormone has a sustained role in sodium regulation and it is responsible for salt retention. It modulates sodium balance by the exchange of sodium and potassium across the distal portions of nephron.

Hypertension can be induced by abnormally increased activity of mineralocorticoids in the body as in primary hyperaldosteronism[28]. The clinical manifestations include arterial hypertension combined with increased aldosterone secretion resulting in the occurrence of hypokalaemia, with characteristic muscle weakness particularly of the neck and proximal parts of limbs, metabolic alkalosis, tetany and polyuria.

The condition is associated with low plasma renin activity and it is due to inhibitory effect of aldosterone on the function of the juxtaglomerular apparatus. There is an inverse relation between aldosterone and renin.

75-80 percent of the reported cases of hyperaldosteronism have occurred in presence of adenoma and remainder have exhibited micronodular hyperplasia of one or both adrenal glands[29]. The severity of the condition is not determined by the size of the adenoma. Mineralocorticoids excess is suggested by the triad of manifestations such as hypertension without oedema, hypokalaemia and low PRA. If hypokalaemia is noted in a hypertensive patient receiving frusemide and thiazides, these diuretics should be discontinued and the patient must receive potassium supplements. If the level of potassium continues to be low after two weeks, then the case has to be evaluted for presence of mineralocorticoid excess.

The diagnosis is established by measuring the secretory rate of aldosterone or aldosterone metabolites in the urine. As the secretion of aldosterone varies periodically, its determination in the plasma is of less value unless it is estimated repeatedly.

Commonly adenoma and adenocarcinoma affect only one of the adrenals. Malignant tumour is associated with irregular fever, abdominal pain, loss of appetite, loss of body weight, and microscopic haematuria. Unlike adenoma, they attain a large size and cause displacement of affected kidney on infusion urogram scan. Retrograde pyelogram shows deformed pyelocalyceal system. Adrenal adenoma is associated with increased aldosterone excretion in the urine. Adrenal carcinoma is associated with excretion of aldosterone and its metabolites and other corticosteroids. There is difference in the plasma aldosterone levels determined in the supine and standing positions. In adenoma the level falls when the patient stands, whereas it increases in those exhibiting hyperplasia.

Low PRA fails to increase during volume depletion including upright position and diuretic administration. Hypersecretion of aldosterone fails to be suppressed during volume expansion (salt loading). Adrenal percutaneous transfemoral bilateral adrenal vein catheterisation with simultaneous adrenal venography helps in the localisation of the adenoma[25]. Adrenal venous sampling shows increased level of plasma aldosterone on the site of adenoma.

Surgery is advised in case of solitary adenoma. However, aldosterone antagonist—spironolactone or potassium-sparing diuretic amiloride or triameterene is advocated in the treatment of mild hypertension associated with adenoma and hyperplasia of adrenal glands.

Deoxycorticosterone (DOC) Excess :

17-Alpha-hydroxylase deficiency: Hypertension can occur in a genetic defect of 17-alpha hydroxylation of deoxycorticosterone[29] . It is associated with pronounced hypokalaemia, excess production of DOC, decreased plasma renin concentration and decreased level of sex hormone precursors. There is improper development of the gonads and secondary sex characters. The condition is treated with glucocorticoids.

11-Beta-hydroxylase deficiency : An increased level of DOC may be noted in a defect in 11-beta-hydroxylation interfering in the conversion of 11-beta-hydroxy cortisol to cortisol and of DOC to corticosterone. A concomitant increased production of androgens may cause virilization during infancy.

18-Hydroxy-DOC excess and 19-hydroxy-DOC excess : Hypertension can develop in presence of excess production of relatively weak mineralocorticoids such as 18-hydroxy-DOC and 19-hydroxy-DOC. Such situations are rare and may be associated with hypokalaemia.

Liddle's syndrome (pseudohyperaldosteronism) : A rare inherited disorder, associated with increased renal conservation of sodium, may occur in presence of negligible aldosterone secretion[30]. The condition manifests with hypertension, hypokalaemia, and decreased PRA. It fails to respond to spironolactone. It responds to administration of 100 mg of triamterene daily as it blocks sodium and potassium exchange in distal tubules.

Cushing's Syndrome

An excess production of glucocorticoids can occur from adrenal hyperplasia secondary to adrenocortical stimulation by increased secretion of ACTH produced by pituitary gland or non-endocrine tumours, or from adrenal neoplasm. The condition may be iatrogenic following prolonged use of glucocorticoids. The condition presents with truncal obesity, hypertension, weakness, hirsutism, glycosuria, abdominal striae and osteoporosis. The retention of sodium is sometimes attended by oedema and decreased renin activity. The levels of plasma cortisol and urinary 17-hydroxycorticoids are elevated.

Pheochromocytoma

Hypertension can result from catecholamine secreting tumours and it may be seen in 0.1% of the hypertensive individuals[31]. 90% of them originate from the adrenal medulla as single, benign tumour. 10% may arise from extradural, neuroectodermal tissue such as paraganglioma associated with cranial nerves, paravertebral sympathetic plexuses, visceral plexuses and plexuses along with the aorta. Generally the condition is noted during middle age. 10% of adrenal tumours are malignant.

The clinical manifestations depend on relative rate of production of adrenalin and noradrenalin by the tumour. However in majority the features are due to a mixture of the two. In those with adrenalin excess, the symptoms are headache, excessive sweating, palpitation, tremors, loss of weight and pallor followed by flushing. In contrast,the symptoms are minimal in those secreting noradrenalin excess. Nearly 50% of individuals have tumours exhibiting their activity in a paroxysmal fashion and there is an increased concentration of catecholamines during such episodes. It is associated with headache, excess sweating, paroxysmal hypertension, tachycardia, orthostatic hypotension and fever. Each attack may last for a few minutes to a few hours. The commencement and disappearance of paroxysms are abrupt. Often they occur without any recognised precipitating factors. However such rapid elevations of blood pressure may be noted during abdominal palpation, postural changes, exercise, surgery, or wearing tight clothing. The individuals often exhibit paradoxical hypertension following administration of beta-blockers and methyldopa.

Familial pheochromocytoma with sustained hypertension may occur as an isolated phenomenon in children and young adults in association with diseases affecting tissues of neural crest origin such as multiple endocrine adenomatosis (tumours of pituitary, parathyroid and pancreas, MEA-I), or medullary carcinoma of thyroid and hyperparathyroidism (MEA-II), or Marfanoid body features, mucosal neuroma and skeletal changes (MEA-III) or neurofibromatosis or von Hippel-Lindau disease (cerebelloretinal haemangioblastoma).

Pheochromocytoma is diagnosed by urinary assays of catecholamines, and their metabolites, vanillylmandelic acid (VMA) or metanephrine. Spot determination of metanephrine has been considered most satisfactory for initial testing and is more sensitive. Its level ranging from 1.0 to 2.2 microgram per milligram of creatinine gives a suspicion of existence of pheochromocytoma. In those with paroxysmal hypertension, urine must be collected when the person is exhibiting hypertension. For spot metanephrine determination, the urine has to be collected during or shortly after the attack. However it is desirable to measure all substances (catecholamines, VMA and metanephrine) if there is a high index of suspicion of pheochromocytoma.

Excretion of urinary catecholamine may be increased during administration of PAS, glyceryl guaiacolate, mephenesin, methyldopa, quinine, tetracycline, erythromycin, chlorpromazine, MAO inhibitors, and during intake of banana, cereals, chocolate, tea, coffee, vanilla and alcohol excess. The level of catecholamines is also increased in severe anxiety states, and circulatory or respiratory failure. The level of VMA may be increased during intake of drugs such as levo-dopa, lithium, nitroglycerin, and nalidixic acid, or decreased during intake of clofibrate, MAO inhibitors and alcohol.

The determination of plasma catecholamines is a difficult and expensive process. The level is elevated during hypertensive episode in presence of pheochromocytoma. The pharmacologic tests to diagnose pheochromocytoma are of limited usefulness and are potentially hazardous. Marked elevation of blood pressure may occur following administration of histamine 0.025 mg intravenously or glucogon 0.5 to 1.0 mg. intravenously. A bolus of 1 mg. alpha-adrenergic blocker, phentolamine, intravenously causes a fall in blood pressure. There is a likelihood of severe hypotensive reaction during such procedure.

The localisation of tumour can be made by intravenous pyelogram and ultrasound if the tumour is large. CT scan helps in visualising the tumour. Arteriography defines the tumour clearly. Selective regional venous catheterisation with assay of venous blood for catecholamines appears to be useful in localising the tumour.

The tumour has to be removed surgically. Alphablocker, phenoxbenzamine,is administered for 1-2 weeks prior to operation. It is begun with 10-30 mg a day and the dose is increased by 10 mg depending on the response.

Toxaemia of Pregnancy

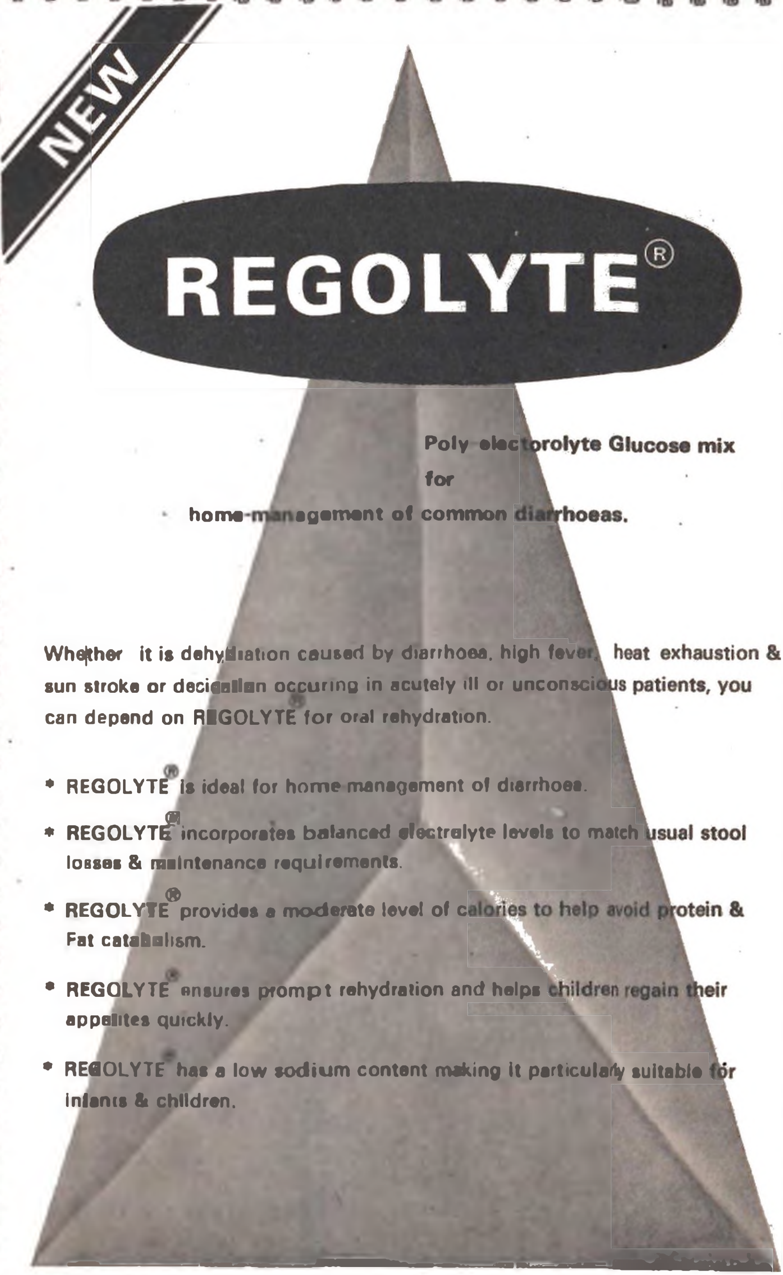
Hypertension in association with pregnancy may be a result of pre-existing hypertension or renal disease or pre-eclampsia and eclampsia. Pre-eclampsia is noted in approximately 5% of pregnant women and is characterised by a triad of hypertension, oedema and proteinuria. However this group may include patients with essential hypertension who develop oedema and proteinuria during pregnancy[32].

Uterus, placenta and kidney appear to be concerned with the production of hypertension. Various factors such as relative uterine ischaemia, impaired uteroplacental perfusion, degeneration of trophoblastic tissue with release of thromboplastin into the maternal circulation, intravascular coagulation, increased production of aldosterone, increased production of renin by chorion and deficiency in prostagladin synthesis by the placenta play a role in the development of hypertension[33].

Coarctation of the Aorta

Constriction of the lumen of the aorta may occur just below the origin of the left subclavian artery. It can occur at the other sites of the aorta rarely. The condition can be associated with other congenital abnormalities of the cardiovascular system such as bicuspid aortic valve, ventricular septal defect, patent ductus arteriosus, or mitral regurgitation.

The condition comes to light due to the presence of hypertension in the upper extremities and cardiac murmurs. Coarctation should be considered if there is a decrease in volume and delay in appearance of pulse in the femoral arteries, markedly decreased arterial blood pressure in the lower extremities and poor development of lower extremities. Presence of collateral intercostal arteries and a midsystolic murmur over the front of the chest and back are noted. Sometimes the patient may complain of fatigue and intermittent claudication.



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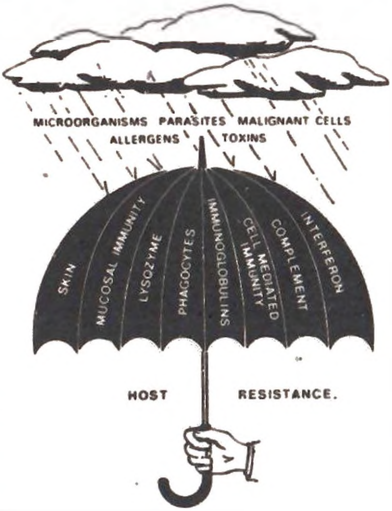
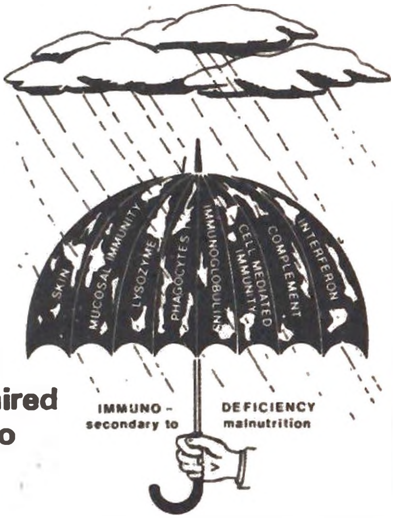


A concert of non-specific barriers and antigen-specific immune responses normally protect man from extraneous and internal injurious agents.

Malnutrition robs the host of these defences.



Rapsovin corrects sub-clinical malnutrition of iron and vitamin B-complex factors.

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RAPSOVIN —a protective umbrella!

Radiogram of the chest shows presence of rib notching, and sharp indentation of the aorta at the site of coarctation with pre- and post-stenotic dilation creating a 'figure 3' sign along the lateral border of the descending aorta. In majority of the patients hypertension is systolic and there is diastolic hypertension if there is involvement of the renal arteries.

The condition requires resection of coarctation and end-to-end anastomosis.

Drug- or Diet- induced Hypertension

Oral Contraceptives : Studies have shown that blood pressure rises in young and middle aged women on oral contraceptives for several years. Hypertension which develops over weeks or months tends to return to pretreatment levels within three to six months after discontinuing the medication. Prolonged intake of oral contraceptives is likely to produce hypertension in about 5% of individuals. This rise in blood pressure is more likely to be related to oestrogen components of the pill[34]. Progesterone is also implicated in the causation of hypertension[35].

Hypertension is more likely in those giving previous history of toxaemia of pregnancy or a family history of hypertension. Obesity, age above 35 years and pre-existing border-line hypertension also influence the degree of blood pressure elevation. It has been shown that the production of hepatic renin substrate is increased following oral contraceptives. There is an increased plasma renin activity and production of angiotensin II and aldosterone resulting in marked vasoconstriction and increased salt and water retention. Even women receiving oestrogens in post-menopausal state are likely to demonstrate an elevation of blood pressure[36].

It is necessary that patients at high risk of hypertension should not use oral contraceptives. The blood pressure should be taken regularly every 6 to 12 months in all women taking oral contraceptives. If hypertension develops, the patients should stop taking contraceptives and use other methods of contraception.

Adrenocorticosteroids : Hypertension can occur as a side effect of long term corticosteroid therapy. Though the extent of rise shows a variability, the pre-existing hypertension or renal disease tend to offer a background for the rise of blood pressure. It is advised that patients on prolonged treatment with steroids, other than for replacement purposes, should get their blood pressure measured at periodic intervals.

Liquorice : An excess ingestion of liquorice (50 to 100 gm/day) as seen in liquorice addicts, may be associated with hypertension and hypokalaemia. Though the clinical picture simulates primary hyperaldosteronism, it can be distinguished by the presence of low aldosterone secretion. The chief ingredient in liquorice, glycyrrhizic acid, exhibits a mineralocorticoid action causing salt and water retention. Carbenoxolone, a synthetic derivative of liquorice used in treatment of peptic ulcer, may exhibit fluid retention, hypertension and hypokalemia[37]. Spironolactone is not advocated for treatment as it may nullify the effect of cabenoxolone on ulcer healing.

Other Pharmacologic Agents : Monoamine oxidase inhibitors used in the treatment of depression prevent the degradation of tyramine and greatly increase its physiologic effect. A tyramine reaction is noted in patients receiving MAO inhibitors whose diet is high in tyramine content (liver, wines and certain types of cheeses). Similar reaction may also be provoked by a variety of sympathomimetic amines (cough and cold cures contain phenyl-propanolamine).

Indomethacin can block prostaglandin release by acting as prostaglandin synthetase inhibitor and contribute to the development of hypertension[38].

MANAGEMENT

Indications :

The dangerous complications and a reduced rate of survival which are associated with persistently raised blood pressure have made it necessary to consider hypertension as a disease and institute treatment. There is a corresponding increase in the complications and mortality from cerebral haemorrhage, left ventricular failure, and progressive renal damage with the increase in the levels of systolic and diastolic blood pressure[39].

It is not proper to delay the treatment till there is occurence of damage to the heart, kidney and brain. By the time these organs exhibit the abnormalities, the condition would have progressed too far. Moreover hypertension is a disorder often not associated with symptoms until the first morbid and fatal episode occurs. Hence it is advised to detect the presence of hypertension at an early opportunity and institute treatment to obtain gratifying results.

Hammer considers hypertension mild when the diastolic pressure is between 90 and 104 mm Hg (by the fifty phase), moderate when the pressure varies from 105 to 114 mm Hg and severe hypertension when the pressure is 115 mm or above[40].

It is necessary to treat all patients who are likely to be benefited from treatment. The clinical trials have conclusively demonstrated the value of treatment in patients with moderate to severe hypertension with a diastolic pressure more than 105 mm Hg, and the treatment is effective in preventing hypertensive complications[41] [42]. However the benefit of therapy in mild uncomplicated hypertension has not been conclusively demonstrated.

In mild hypertension, the major cardiovascular complications are primarily atherosclerotic and sudden death and myocardial infarction are frequent. In moderate-to-severe hypertension the compilcations are due to hypertension and also due to atherosclerosis. The former includes congestive heart failure, renal failure, cerebral haemorrhage, subarachnoid haemorrhage, malignant hypertension and dissecting aortic aneurysm. Hypertension detection and follow-up program (HDFP) claimed significant reduction of fatal coronary heart disease with antihypertensive therapy in mild hypertension[41]. However the trials conducted in Australia, Norway and US (multiple risk factory intervention trial, MRFIT) have shown that the treatment has no effect on cardiovascular morbidity and mortality in borderline-mild group of hypertension[44] [45] [46].

Framingham study has shown that it is advisable to treat only those patients with mild hypertension who are having great risk of cardiovascular complications[47]. The group includes patients with large number of risk factors in addition to hypertension such as cigarette smoking, increased levels of cholesterol, decreased level of high density lipoproteins (HDL), electrocardiographic evidence of left ventricular hypertrophy and diabetes mellitus.

However experience has shown that it is advisable to treat all patients with a diastolic blood pressure above 90 mm Hg regardless of age. The goal of treatment is to achieve a normotensive or near normotensive blood pressure with administration of antihypertensive agent,alone or in combination,for life.

THERAPEUTIC APPROACH

The patient receives a therapeutic combination of drugs by way of stepped care or the therapy of specific mechanisms. Stepped care treatment is based on the sequential addition of drugs until the blood pressure is lowered to an acceptable level[48]. Such a treatment has been found useful in mass treatment of mild to moderate hypertension; the hypertensive mechanism has to be attacked at different sites using a combination of several drugs each having a different mode of action. Therapy based on specific mechanisms enables the physician to undertake a rational approach to the more complicated problem. However these two modes of treatment are complementary to each other[49].Experience has shown that a combination of drugs with different mechanisms of action provide better results. The side effects are also minimal with such a therapy.

The stepped care method of treatment involves stepwise addition of drugs in a 'building block' fashion to achieve reduction of blood pressure. An approach to the problem is made beginning with mild drugs (diuretics) to be followed by addition of adrenergic inhibitory drugs, vasodilators or other potent agents in a step-wise fashion if the initial therapy has not brought about the desired response (table III).

Stepped care therapy is a good way to approach the problem of hypertension and it gained prominence with the advent of diuretics, reserpine and vasodilators. Stepped care therapy recommended by the Joint National Council on Detection, Evaluation and Treatment of High Blood Pressure, is based on the fact that if the use of one antihypertensive is unable to bring down the diastolic pressure to 90 mm Hg or below, the therapy has to be stepped up with additional antihypertensive agents[48]. Such stepped care has a pressure of 'step down', which implies that,if the blood pressure has been well controlled over a period of 6 to 12 months, the antihypertensive agents may be discontinued step by step and control of the blood pressure may be achieved with minimal therapy[49].

Table III : Stepped-Care Regimens

Step	Drugs
1.	Diuretic
2.	Adrenergic inhibiting agents Rauwolfia alkaloids Methyl dopa Beta-adrenergic blocking agents—propranolol, metoprolol, nadolol, pindolol, atenolol, timolol Clonidine hydrochloride Prazosin hydrochloride
3.	Vasodilators Hydralazine hydrochloride Prazosin hydrochloride
4.	Additional adrenergic inhibiting agent Guanethidine sulphate

There is need to treat many hypertensive individuals on life-long drug therapy. The drugs used must be effective in reducing the blood pressure without causing any serious side effects. Kruck has suggested a regimen (i) using drugs according to their main action and according to predominent features considered to be the main cause of the rise of the blood pressure, (ii) to combine drugs with different mechanisms of action to reduce the doses of each drug thus diminishing the side effects and (iii) to avoid centrally acting drugs or if used, use in very low doses.

Though diuretics are the drugs of first choice in antihypertensive therapy, they are less effective in younger patients especially those with early or borderline hypertension, who frequently exhibit signs of sympathetic overactivity. The condition is associated with increased concentration of noradrenalin and high plasma renin activity. Studying renin profile, Laragh advocated the use of beta-blocking drug initially in the treatment[50]. Sympathetic overactivity causes a rise in blood pressure in a stepwise fashion by its effects on heart and blood vessels. Only in later stages is kidney continuously influenced by raising blood pressure and ultimately it becomes the main source for persistent hypertension. By that time the sympathetic overactivity becomes less apparent. The high renin hypertension encountered in young patients shows a decline with increasing age.

Diuretics are the drugs of first choice in patients with sustained hypertension and low plasma renin, or in elderly patients. There is an increased extracellular fluid volume or decreased sympathetic activity or both in low renin hypertension. Generally thiazide diuretics are used as long as kidney function is well preserved. It is only in situations of decreased glomerular filtration, that loop diuretics are used as they are still capable of eliminating salt and water. In addition, diuretics counteract salt and water retention caused by other antihypertensive agents. If the blood pressure has not come down, beta-adrenergic blocking agents or other adrenergic inhibiting agents are added to the regimen to achieve the goal of therapy. Vasodilators are used when the combination of diuretic and adrenergic inhibiting agent is not able to reduce the blood pressure by decresing peripheral vascular resistance. In those not showing much response, addition of other adrenergic inhibiting agents such as guanethidine is made.

Messerli has advocated the need for individualization of antihypertensive therapy based on the haemodynamics and age. A beta-blocking agent is suggested for borderline and early hypertension and a combination of a thiazide type of diuretic and an adrenergic inhibiting agent for those with established essential hypertension[51]. Now concern has been expressed about the initial use of a diuretic as the first step in therapy of hypertension due to its side effects[52]. Beta adrenergic inhibiting agents, even though effective in decreasing the blood pressure, tend to increase the peripheral vascular resistance. Other adrenergic blocking agents show a tendency to retain sodium and water, thus blunting their effectiveness.

The side effects of diuretic therapy are hypokalaemia, hyperuricemia, hypercalcemia, decrease in glucose tolerance and increase in plasma cholesterol. The biochemical aberrations are likely to increase cardiovascular risk, especially coronary artery disease. The trials have shown that diuretics may provide less protection from the progression of coronary artery disease[52]. They protect from cardiovascular diseases in individuals with diastolic pressure greater than 104 mm Hg. However those with blood pressure ranging between 90 and 104 mm Hg are at less risk from hypertension. The amount of protection from a reduction in the blood pressure is far less compared to those with higher pressures.

The initial drug used must be safe and without any side effects.

The occurrence of fluid retention is less common with beta blocking drugs compared to other agents and is due to marked inhibition of the renin-angiotensin-aldosterone system. Though the long range stimulus to atherogenesis, like increased plasma triglyceride and decrease in plasma HDL, are less marked with more cardioselective beta-blocking drugs, they produce an increased peripheral vascular resistance. It is due to blockage of peripheral vascular beta receptors. It becomes a problem in colder climates where cold extremities are frequently seen.

Prazosin has been shown to be an effective and well tolerated agent when used as initial therapy in all grades of hypertension. It lowers blood pressure by reducing total peripheral resistance. It has no adverse effects on lipid, glucose or uric acid metabolism, frequently seen with diuretics[53].

Substitution therapy is preferable in some patients as they show good response to one group than to another group of drugs. Though all antihypertensive agents have comparable potency, response shown by the patients varies to different drugs. Observations have shown that beta-blocking agents may not be effective in elderly. However they are effective in young patients and they show better response to beta blocking agents than to diuretics[54]. As it is not possible to predict the response the physician has to use different type of agents when the first drug has proved to be inadequate. Kaplan has observed that when a patient does not showthe desired effect from the initial antihypertensive agent, a logical next step might be to stop the drug and try one from another group of antihypertensive agents.[52] This will enable to achieve the goal of therapy with fewer medications. It gives the freedom to the physician to choose the drug that will be safe in the long run.

Looking at the availability of a variety of anti-hypertensive agents, and the regimens, Cutler has said that we have now reached the point where the menu of therapeutic agents is quite large, and, as when we visit a favourite restaurant, we probably need to pick and choose more appropriately, depending on the patient and the problem at hand[55]. He has appropriately pointed out that it is no longer starting from one place and moving to another, but to think of the pharmacologic effects of each drug and use it appropriately in treating a particular patient.

NONSPECIFIC METHODS OF TREATMENT

The, nonspecific or non-pharmacologic methods of treatment have shown to be effective in reducing mild elevation of blood pressure and in delaying the necessity for institution of pharmacologic therapy. In addition they act as adjunct to specific or pharmacologic therapy, wherein they tend to reduce dosage and side effects of drug therapy. Generally the nonspecific methods are advocated as initial therapy. The three major nonspecific approaches are diet, physical exercise and behavioural modification.

Diet :

Since the introduction of diuretics, a strict salt restricted diet is not needed. However a modest restriction of salt intake (from 10 to 12 grams a day to 2 grams or below),achieved by avoiding salty foods, avoiding addition of salt to the food and by not adding salt at the table, was shown to reduce blood pressure on an average by 10 to 15 mm Hg in at least 50% of mild hypertensives[25].

A young, borderline or mild hypertensive should have modest salt restriction throughout his life. Salt restriction in patients receiving thiazides minimises the kaliuretic effect of the diuretic. It also plays a significant role in patients who exhibit low-renin hypertension and occasionally in patients who have severe or refractory hypertension. There is need to create an awareness that excess salt intake can be harmful to some persons. As the taste for salt is developed, many patients find difficulty in reducing the salt intake. Sometimes it can be substituted by potassium chloride in part or total[56]. Though it may be helpful in some, it may have adverse effect in those with undiagnosed renal insufficiency.

There is need to limit intake of animal fat in presence of hypercholesterolaemia and the patient must be advised to stop smoking. Reduction of these risk factors is likely to have a synergistic action in delaying atherosclerotic changes in the individual.

Weight Reduction : Chiang et al have shown a relationship between obestity and hypertension[57]. Weight reduction by calorie restriction is often associated with a reduction of blood pressure. However attention has to be given to the 'fat arm' of the obese patients which is likely to give erroneously high readings for the blood pressure when routine cuff is used. A correction for 'fat arm error' has been advocated on the basis of arm circumference or body weight when a conventional cuff is used[58].

Physical Exercises : Physical conditioning from regular isotonic exercises (skeletal muscles change in length with little change in tension) such as jogging and swimming cause increased heart rate and cardiopulmonary changes with production of peripheral vasodilatation which tends to decrease blood pressure. The study of long term haemodynamic effects of such exercises has shown a significant reduction in diastolic pressure in hypertensives.

Behavioural Modification: As behavioural stress and emotional tension are considered as aetiologic factors in the production of hypertension, attempts are to be made to lower the blood pressure by psychotherapy, behavioural modification and biofeed-back techniques.

Psychotherapy has been used since a long time in the management of hypertension. The patients are to be reassured. Behavioural modification with rest and relaxation, change in the mode of life, shortening of the hours of work, change in the tempo of work, development of hobbies, avoidance of controversial discussions and excitement, avoidance of tensions, practice of yoga and transcendental meditation are likely to cause mild reduction in blood pressure[59 60].

Sedatives and tranquillisers show little antihypertensive effect. Hence such drugs are not considered part of routine treatment for hypertension. Yoga helps in modifying the effects of stress. Practice of shavasan has shown to bring down blood pressure and decrease the dose of antihypertensives required. Transcendental meditation helps in achieving relaxation. The constant chanting of mantras enables the person to be free from externally oriented thoughts. With relaxation, it is possible to bring about physical and emotional calmness and decrease sympathetic arousal, and in turn lowering of blood pressure.

The feedback of moment-to-moment biological information to a patient about a specific physical process taking place under the control of nervous system is utilised in the management of hypertension. Using instruments, it is possible to give visual perception of weight, diastolic blood pressure and electromyographic feedback. Though Frankel et al could not demonstrate significant decrease in persistent high blood pressure with a combination of diastolic blood pressure feedback, electromyographic feedback and relaxation techniques, they observed increased ability to relax and to cope with stressful situations and even relief from muscular tension headache[61]. Probably the relaxation and biofeedback techniques appear to be of value in patients who tend to be anxious or tense, and in young patients with mild hypertension. However it is doubtful how long their effect is maintained. These techniques can be employed only as adjunct for patients already undergoing drug therapy.

PHARMACOLOGIC THERAPY

Antihypertensive Drugs :

The antihypertensive drugs are broadly classified as diuretics, adrenergic blocking drugs, vasodilators, calcium channel blockers, and selective antagonists (table IV).

Table IV : Antihypertensive drugs

1. Diuretics
   Benzothiadiazine and related compounds, loop diuretics, potassium sparing natriuretic agents
2. Adrenergic or sympathetic blocking drugs
   Central : alpha-methyldopa, clonidine. Peripheral: reserpine, guanethidine, debrisoquin, ethanidine
   Autonomic ganglia: mecamylamine, pentolinium, trimethophan
   Beta-receptors: propranolol, metaprolol, nadalol, atenolol, timolol, pindalol
   Alpha-receptors: phenoxybenzine, phentolamine, indoramin
   Alpha and beta receptors: labetalol
3. Vasodilators:
   hydralazine, minoxidil, prazosin, diazoxide, nitroprusside
4. Calcium channel blockers: nifedipine

5. Selective antagonists:
   i) converting enzyme, captopril
   ii) angiotensin II, saralasin

Diuretics :

Diuretics are used as the first step in the treatment of hypertension alone, and in subsequent steps their use has added advantage of potentiating the action of other antihypertensive agents thus enabling reduction of their dose or even stoppage of one agent when several antihypertensive preparations have to be administered simultaneously.

The diuretics affect the blood pressure in three ways. They increase sodium diuresis by acting on the renal tubules and reduce extra-cellular fluid volumes and the cardiac output. They also decrease the total peripheral resistance on long term use. They prevent the salt and water retention which occurs as a physiologic side effect of the vasodilators or sympathetic depressants except the beta-blockers.

The diuretics that are commonly used in the treatment of hypertension are shown in table V.

Table VI : Diuretics

1. Benzothiadiazine and related compounds
    - Thiazides
    - Metolazone
    - Xipamide
    - Indapamide
2. Loop diuretics
    - Frusemide
    - Ethacrynic acid
    - Bumetanide
3. Potassium sparing agents
    - Spironolactone
    - Triamterene
    - Amiloride

Diuretics act at different parts of the renal tubules. The thiazides and other related compounds act in the terminal portion of ascending limb and initial portions of distal tubules (cortical segment); the loop diuretics act in the loop of Henle and ascending limb. The potassium sparing agents act in the distal tubules.

Benzothiadiazine and related compounds : A large number of benzothiadiazine agents have been produced by varying the structure of the basic formula. Though they vary in their dose and duration of action, depending on their protein binding capacity and renal tubular reabsorption, there is no advantage of one drug over another in terms of their potency, saluretic activity and antihypertensive effect and side effects[62]. These drugs are well tolerated and occasionally may cause dizziness, nausea, weakness, fatigue, gastric irritation and muscle cramps.

Benzothiadiazine and phthalimidines (chlorothalidone) have relatively flat dose response curves[62] and the same dose can be given for all patients. Beyond the equivalent of 150 mg. hydrochlorothiazide the dose response is same with all benzothiadiazine derivatives[63]. There is no benefit by using a large dose. Long term therapy is associated with progressive rise in the level of plasma renin and it may limit its diuretic action. Generally thiazides are administered in the morning as a single dose, and when necessary the second dose can be given early in the afternoon. Hydrochlorothiazide can be given in a dose of 50 mg twice a day. Similarly bendrofluazide is given 5 mg twice a day and cyclopenthiazide 0.5 mg twice a day. The longer acting drugs such as chlorothalidone 100 mg, and polythiazide 2 mg are administered once a day.

Metolazone, though chemically different, has action similar to that of thiazide. It has a rapid onset of action and longer duration of action. It is administered in a dose of 2.5 to 5.0 mg and is useful in those showing allergy to thiazides and renal failure[64].

Xipamide is a potent and long acting diuretic and may be more effective than thiazide[65]. Essentially it acts on the distal tubules and it is administered in a dose of 20 mg as a single dose. Indapamide, a thiazide analogue, has diuretic and vasodilator properties[66]. It is administered in a dose of 2.5 mg daily and it is not administered in severe renal or hepatic insufficiency.

Rarely the diuretics can produce hypersensitivity reaction. Long term therapy may lead to hypokalaemia, and very rarely hyponatraemia if there is severe dietary sodium restriction, or coexisting renal insufficiency. There can be overt diabetes in those predisposed to impaired glucose tolerance and hyperuricemia. These side effects are not common and there is no need to use potassium supplements routinely. If the patient restricts intake of salt, hypokalaemia is not a problem.

Diuretics do not show any improvement in coronary disease. Rise in cholesterol and low density lipoprotein fractions and fall in high density lipoprotein fractions affect adversely the coronary heart disease[67]. Though the results of hypertension treatment trials using diuretics as first line therapy show a reduction in stroke and congestive heart failure, coronary heart disease is most consistently benefited and is probably due to alteration in the metabolic risk factors.

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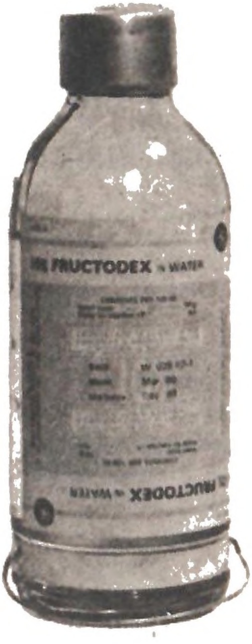
—‘Advances in Parenteral Nutrition’ Ed. Ivan D.A. Johnston, MTP Press, 1978.



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Loop diuretics : Loop diuretics inhibit absorption of sodium and are effective in patients with moderate or severe renal failure[68]. Frusemide is administered in a dose of 40 to 80 mg a day. It has a steep dose response curve and has short duration of action. Though it reduces extracellular fluid volume of heart failure or cirrhosis, it is not so effective in hypertension[69]. Ethacrynic acid (50-200 mg) may produce gastro intestinal side effects and transient loss of hearing. Bumetanide is a powerful diuretic in a dose of 1-2 mg. It has an action for 6 to 8 hours. Loop diuretics are not convenient to use alone as a first step in therapy.

Potassium sparing diuretics : Spironolactone is an antogonist of aldosterone, whereas triamterene and amiloride act on the kidney independently of aldosterone. They inhibit sodium-potassium exchange in the distal tubules. They are weak diuretics and mild antihypertensive agents. They are used in the treatment of hypertension mainly in combination with other diuretics to prevent excess hypokalaemia. There is no need for potassium supplements while the patients are taking these drugs.

Spironolactone is administered in a dose of 25 mg four times a day, triamterene 100 mg twice a day and amiloride 5 mg twice a day. Spironolactone is specific in the treatment of primary and secondary aldosteronism. Spironolactone is not indicated in patients with renal failure or imparied renal function as there is danger of hypokalaemia. Due to alteration in testosterone metabolism spironolactone may produce gynaecomastia and decreased libido.

ADRENERGIC BLOCKING DRUGS

Alpha Methyldopa : Alpha methyldopa is a centrally acting adrenergic blocking drug with primary site of action in the central nervous system[70]. It blocks the decarboxylase enzyme which is responsible for conversion of dopa (3,4 dihydroxy phenylalanine) to dopamine (3,4 dihydroxy phenyl amine), an immediate precursor of noradrenalin, and of 5 hydroxytryptophane to 5 hydroxytryptamine. It also forms a false transmitter from decarboxylation of methyldopamine and its subsequent metabolism to methyl noradrenalin which in turn displaces noradrenalin from the nerve terminals. It decreases the renin release from the kidney.

The peripheral effects of methyldopa appear to be centrally mediated by a mechanism which decreases sympathetic vasomotor outflow by stimulating post-synaptic alpha receptors in the vasomotor centres of the brain[71]. It decreases peripheral arteriolar resistance without any effect on heart rate or cardiac output. It does not affect renal blood flow.

Alpha methldopa is administered in a dose of 250 mg twice or thrice a day which can be increased to a maximum of 2 grams in a day. A single dose is effective for 8 hours. It can be administered intravenously in a dose of 0.5 to 1.0 Gm every 4 to 6 hours during treatment of malignant hypertension. It reduces peripheral resistance with minimal reduction of cardiac output. In situations when the blood pressure is not lowered, oral diuretic added as methyldopa is likely to cause fluid retention with expansion of plasma and extracellular fluid volume. The drug is indicated in moderately severe or severe hypertension including situations with renal insufficiency. It brings down blood pressure without much haemodynamic disturbances. Orthostatic hypotension is less frequently encountered.

Dry mouth, marked drowsiness, weakness, depression, headache, arthralgia, gynaecomastia, lactation, weight gain, acute febrile episodes, and rarely Parkinsonism may occur as side effects. Rarely it can produce hepatitis, and serious 'autoimmune' reactions such as positive direct Coomb's test, positive antinuclear antibody and haemolytic anaemia.

It produces marked drowsiness in the initial stages of treatment and generally it subsides in about a week. In some patients sedation and mental dullness may interrupt their activity during daytime. It is contraindicated in depressive states, in liver diseases, pheochromocytoma, and during administration of monoamine oxidase inhibitors. Caution has to be taken while administering methyldopa in situation of angina and congestive heart failure[70].

Clonidine :

Clonidine acts by directly stimulating central alpha adrenoreceptors in the hind brain and by reducing the sympathetic tone of central nervous system[72]. It also acts peripherally on alpha adrenoreceptors and directly on vascular smooth muscles to result in vasodilatation and decrease in peripheral resistance. It does not affect the renal blood flow or the glomerular filtration rate.

Along with a diuretic, clonidine acts as an effective antihypertensive agent. On oral administration clonidine brings down the blood pressure within 30 to 60 minutes, and its peak action is reached within 2 to 4 hours. It is administered in a dose of 0.1 to 0.3 mg thrice a day. It does not produce postural and exertional hypotension. It produces drowsiness, dryness of the mouth, constipation and decreased libido. These side effects are dose related.

In addition it has a peculiar side effect or rebound hypertensive crisis simulating a pheochromocytoma attack. It is noted when the administration of the drug is discontinued abruptly. The patient may experience marked elevation of blood pressure, tachycardia, palpitation, sweating and feeling of anxiety[73]. There is an increase in plasma and urinary catecholamines. The manifestations are relieved by parenteral administration of clonidine in a dose of 300 micrograms.

Reseprine :

Rauwolfia alkaloids are centrally and peripherally acting adrenergic blocking drugs and are useful in mild to moderate hypertension. They decrease the sympathetic tone by depleting catecholamines in the brain, and in the post-ganglionic adrenergic nerve endings[74]. They prevent the re-uptake of released noradrenalin into the storage vesicles, and facilitate its degradation. They have a direct effect on vascular smooth muscle when given parenterally. They decrease peripheral vascular resistance, decrease heart rate and cardiac output by decreasing sympathetic nervous system activity on the blood vessels and the heart. There is decreased plasma renin activity.

Among the alkaloids isolated from Rauwolfia serpentina, reserpine is the most potent. Incidentally it was the first of the orally effective antihypertensive agents to be widely used. It is given in a daily dose of 0.1 to 0.75 mg orally. The onset of action is seen after 5-7 days. Reserpine can also be given parenterally in a dose of 0.5 to 1.0 mg intramuscularly in hypertensive emergencies, where it shows its effect in 3 hours.

Reserpine is contraindicated in pheochromocytoma, peptic ulcer, depression and during MAO inhibitor administration. The drug is mildly sedative. Side effects include nasal congestion, mental depression, dyspepsia, diarrhoea, decreased libido and Parkinson-like syndrome. Sometimes mental depression will be so severe as to cause suicidal tendency. There is a likelihood of an increased incidence of breast cancer in women receiving the drug overa long period[75]. However such fear appears to be unfounded.

Adrenergic Neurone Blockers :

Adrenergic neurone blockers are potent post-ganglion adrenergic blocking drugs and act as powerful antihypertensive agents. The group includes guanethidine sulphate, bethanidine sulphate and debrisoquin sulphate[76].

Guanethidine :

Guanethidine inhibits sympathetic activity at the peripheral nerve terminal. It acts by inhibiting release of adrenergic effector substance, noradrenalin and causes its depletion at the storage sites. It blocks the re-uptake of noradrenalin.[77] Further it decreases plasma renin activity.

Guanethidine reduces heart rate, cardiac output and peripheral resistance. There is modest fall in blood pressure in the recumbent position. But the fall is great while the patient is standing. The duration of action is 24 to 72 hours and it is administered orally once a day. It is begun in a dose of 10 mg a day and slowly titrated upto a maximum of 200 mg. Tricylic antidepressant drugs and amphetamines counteract the antihypertensive action of guanethidine as they get concentrated at the peripheral nerve terminals. Postural and exertional hypotension are frequent.

Fatigue, diarrhoea and ejaculatory failure are other important side effects. It does not have any central nervous system side effects such as sedation or depression as it does not cross the blood brain barrier. The side effects have restricted its use in situations of severe hypertension. Caution has to be taken while administering the drug in cerebral or coronary atherosclerosis and renal disease, cerebrovascular insufficiency, renal disease and pheochromocytoma. Guanethidine is not useful in situations where the blood pressure shows an acute rise as there is need to build up an effective dose.

Bethanidine :

The congener of guanethidine, bethanidine has similar mode of action as guanethidine[78]. It has a rapid action beginning in 1 to 2 hours and reaching a maximum in 4 hours and the duration of action is for 8 to 12 hours. The drug is administed in a dose of 10 mg thrice daily, and it may be increased to a total daily dose of 50 to 100 mg. The drug can be given in acute hypertension. It has less tendency to produce diarrhoea and ejaculatory failure.

Debrisoquin :

Debrisoquin exhibits action similar to that of guanethidine[79]. It is administered in a dose of 40 to 80 mg a day. It has certain limitations as an antihypertensive as it affects orthostatic rather than recumbent blood pressure.

Autonomic Ganglion Blocking Drugs :

These drugs block the receptors on ganglion cells and prevent the action of acetyl choline on sympathetic and parasympathetic nerves. The lowered sympathetic tone decreases cardiac output and increases peripheral vasodilation. Adrenergic ganglion blocking drugs include secondary amines (mecamylamine), tertiary amines (pempidine and trimethophan), and quarternary ammonium compounds (hexamethonium, pentolinium and chlorisondamine). The parasympathetic blockade causes undesirable side effects. Hence these drugs are rarely used in routine therapy except in hypertensive crisis.

Postural hypotension, syncopal attacks, constipation, urinary retention, dry mouth, blurred vision are common side effects.

Beta-Adrenoceptor Blocking Drugs

Since the establishment of the antihypertensive property of propranolol, a variety of beta-adrenergic blocking drugs are available[80]. They differ in their associated properties such as cardioselectivity, membrane stabilising activity (MSA), intrinsic sympathomimetic activity (ISA), lipid solubility, and plasma protein binding capacity[81].

The beta-adrenoceptor blocking drugs are broadly grouped into 3 divisions as those without any cardioselectivity, those with cardioselectivity and those possessing alpha-adrenergic blocking properties[82]. The non-selective agents block both beta (beta$_1$ and beta$_2$) receptors. They may possess both membrane stabilising and intrinsic sympathetic activity (alprenolol, oxprenolol), membrane stabilising action only (propranolol), intrinsic sympathetic activity without membrane action (pindolol) or may lack membrane action and ISA (sotalol, nadolol, timolol). The cardioselective agents selectively block $beta_1$ receptors without affecting $beta_2$ receptors. They may exhibit both membrane action and ISA (acebutolol) or only ISA without membrane action (practolol) or may exist without sympathetic activity or membrane action (atenolol, metoprolol). Lebetalol is a beta-adrenoceptor blocking drug possesssing alpha-adrenoceptor blocking property.

These drugs bring about reduction in blood pressure by their effect on central nervous sympathetic tone, adrenergic neurone blocking effect, suppression of renin release, reduction of cardiac output and by a mechanism consequent on resetting the baroreceptors[82]. The hypotensive effect is noticed regardless of associated properties, the presence or absence of membrane stabilising or intrinsic sympathetic activity.

Propranolol has been extensively used as an effective antihypertensive agent in a dose of 40 mg to 240 mg in divided doses. It produces a gradual and smooth fall in blood presure. It blocks both central and peripheral beta receptors. Through its action on cardiac sympathetic innervation, it brings down the heart rate and decreases cardiac output. Propranolol is highly protein bound in plasma and is lipid soluble. Metaprolol (100-400 mg) and atenolol (50-100 mg) are relatively cardioselective and their effect is essentially on beta rather than $beta_2$ receptors. Nadolol (80-320 mg) and atenolol possess relatively minimum lipid solubility and have minimal plasma protein binding capacity. They are excreted mainly through the kidney. They exhibit prolonged action mainly through the kidney and they get accumulated with renal failure. Pindolol (15-45 mg) causes less reduction in cardiac rate due to its intrinsic sympathetic activity.

Beta-blockers get metabolised during absorption. Hence it is difficult to predict their effect with a standard oral dose and the dose had to be adjusted individually. A progressive increase in dose is needed to obtain an optimal response. They offer relief from anxiety-related symptoms. Hence they can be given alone in young patients with labile or border-line hypertension who show a rapid pulse rate and hyperkinetic circulation. Thus they are often used as the first step drug instead of diuretics in treating such patients. As they bring down the cardiac output, they offer a distinct advantage during early stages of the disease when the cardiac output may be high with normal peripheral resistance. They are employed in those with documented raised plasma renin activity[83].

Long term use of beta-blockers exhibit cardioprotective and vasculoprotective effect such as reduction of tachycardia and arrythmias, reduction in size of myocardial infarction and reduction in the recurrence of myocardial infarction[84]. Thus they offer possible protection from coronary heart disease. They don't cause any sedation. They do not exhibit postural or exercise hypotension. There is less tendency for retention of sodium and water. The effectiveness of beta-blockers is enhanced when they are used with vascular smooth muscle relaxants and diuretics.

The side effects are bradycardia, bronchospasm, heart failure, peripheral vasoconstriction, reduced exercise tolerance, fatigue, depression, insomnia, nightmares and decreased libido. As they increase triglyceride level and decrease HDL-cholesterol, there is possibility of their acting as long term stimulants to atherogenesis[85]. These drugs are not so effective in elderly and in those with atherosclerotic heart disease as they can precipitate heart failure. The increased airway resistance can induce bronchial asthma in susceptible individuals.

Beta-blockers raise the peripheral vascular resistance due to blockade of vasodilatory peripheral vascular beta-receptors and it will cause a problem in those living in colder climates as they exhibit cold extremities[86]. In individuals with bronchial asthma and peripheral vascular disease, cardioselective agents are useful. However their antihypertensive property is not greater than non-selective agents. Great caution has to be exercised when beta-blockers are used in diabetics receiving hypoglycemic agents, as they inhibit sympathetic response to hypoglycemia. Practolol is not used as an antihypertensive agent due to its side effects such as dry eyes, corneal ulcers, SLE syndrome and sclerosing peritonitis.

Labetalol has lesser effect on cardiac rate and less effect on airway resistance. It reduces peripheral resistance. It is administered in a dose of 300-400 mg. It produces postural hypotension in larger doses[87].

Alpha-Receptor Blocking Drugs :

These drugs block the action of circulating noradrenalin at pre-

and post-synaptic alpha adrenergic receptor sites. Phenoxybenzamine, phentolamine and indoramine belong to this group. The long acting phenoxybenzamine is given in a dose of 20-60 mg once a day and it has a duration of action for a week. Short acting phentolamine can be administered in a dose of 200-300 mg in divided doses a day. A bolus intravenous dose of phentolamine (2-10 mg) is used in hypertensive crisis and suspected pheocyromocytoma. Indoramin is administered in a dose of 50-200 mg to lower the peripheral resistance.

The frequent association of side effects such as postural hypotension, tachycardia, weakness, dizziness, impotence and relative fluid retention have limited their usefulness in therapy of hypertension. Indoramin does not produce postural hypotension[88]. The use of alpha-receptor blocking drugs is limited in acute hypertensive states and in the diagnosis and preoperative treatment of patients with pheochromocytoma. These drugs are contraindicated in severe coronary artery disease.

VASODILATORS

Hydralazine

Hydralazine hydrochloride is a potent vasodilator. It causes direct relaxation of arteriolar smooth muscle at precapillary level and lower peripheral vascular resistance. Ther is reflex sympathetic stimulation from vasodilation to result in increased heart rate, stroke volume and cardiac output[89].

It is useful in moderate to severe cases of hypertension. Its antihypertensive potency is weak when used alone, and often it is used to potentiate the effect of beta-blockers, or sympatholytics or diuretics in bringing down the blood pressure. In such combinations, the sympatholytics or beta-blockers prevent reflex tachycardia, and diuretics prevent excessive fluid retention which occurs following administration of hydralazine.

Hydralazine is administered in a dose of 25 to 50 mg twice a day and the dose is increased at weekly intervals until there is an adequate response[90]. A maximum of 200 mg a day may be given. It can be given parenterally (intramuscular or intravenous) in a dose or 10 to 50 mg every six hours in the treatment of malignant hypertension.

Palpitation, dyspnoea, angina, headache and diarrhoea can occur as important side effects. These side effects tend to disappear as the administration of the drug is continued. A lupus erythematosus-like syndrome may occur when large doses of hydralazine are used in the treatment over a long term.

Hydralazine can reduce 10-20 mm Hg of blood pressure; however the effect is relatively unpredictable in the individual patient[49]. It is necessary to evaluate patients for evidence of coronary insufficiency or congestive heart failure prior to administration of hydralazine as it has a direct cardiac stimulant action[89].

Minoxidil

Minoxidil is a powerful vasodilator, directly causing relaxation of arteriolar smooth muscle[91]. Its hypotensive action is more potent and longer acting than that of hydralazine. It is advocated in situations of very severe and refractory hypertension as seen in patients with chronic renal diseases, advanced connective tissue disorders or malignant hypertension. It readily brings down the diastolic blood pressure. The fall in peripheral resistance is associated with a reflex tachycardia and increased cardiac output. It also results in retention of sodium, and there is an associated rise in plasma renin.

The side effects are similar to those noted on administration of hydralazine. Such problems are managed by simultaneous administration of diuretics and beta-blockers. Minoxidil does not lower glomerular filtration rate or renal plasma flow, and hence its use is mainly limited in individuals with faulty renal function, who have not shown response to combination therapy of antihypertensive agents. It is also advocated in patients with high renin level associatedc with chronic renal failure[92].

Minoxidil is rapidly absorbed on oral administration and the hypotensive action is noted within 2 hours, and it lasts for 6-8 hours. It is administered in a dose of 5 to 30 mg a day. The concomitant fluid retention and tachycardia associated with minoxidil are managed by using the drug in combination with a diuretic and beta-blocker.

Fluid retention and hirsutism occur as major side effects. Tachycardia and angina are also noted. Hence there is need to assess for presence of coronary insufficiency. Occurrence of hirsutism and

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associated coarsening of facial features have significantly limited its use in women.

Prazosin :

Prazosin hydrochloride is a sympatholytic agent. It exerts its antihypertensive effect by direct relaxation of vascular smooth muscle and by selective post-synaptic $alpha_1$ adrenergic blockade[93]. It has an inhibitory action on phosphodiesterase in the arteriolar smooth muscle and facilitates accumulation of cyclic AMP. It lowers systemic vascular resistance and controls the blood pressure without inducing reflex cardiac stimulation. As the presynaptic $alpha_2$ receptors on the neuronal surface are not blocked the feedback loop for inhibition of noradrenalin release remains intact and there is no reflex tachycardia. The cardiac output is not reduced. The renin release is not increased. Such side effects are frequently noted with direct-acting vasodilators. The renal blood flow and glomerular filtration are unaffected[94].

Prazosin is well absorbed on oral administration and its antihypertensive effect develops gradually. Its action is not closely related to plasma level as the drug gets bound in the arteriolar walls. It is administered in a dose of 2 to 10 mg. The dose is gradually stepped up. The antihypertensive effect of prazosin is enhanced when it is used with a diuretic or with a beta blocker. Prazosin is often used in situations of severe hypertension not responding to diuretics and beta-blockers. It is effective in patients with renal insufficiency. It does not adversely affect lipid values[95]. It may be especially useful in patients with hypertension and congestive heart failure as it reduces the afterload, and also preload by dilating venous bed in the latter situation.

Postural hypotension and syncope occur as major side effects. They are especially noted after the first dose; then those manifetations gradually subside. However such side effects are noted when the drug is given to patients who are volume depleted from previous diuretic therapy[96]. The side effects are prevented by administration of the first dose at bedtime and in a dose of 1 mg. The side effects are prevented by administration of the first dose at bedtime and in a dose of 1 mg. Some patients complain of headache, weakness, fatigue and a feeling of incoordination following administration of prazosin.

Prazosin is now frequently advocated as initial therapy along with sodium restricted diet[52].

Calcium Channel Blockers

The contraction and relaxation of vascular smooth muscle is dependent on increase or decrease of intravascular calcium respectively. The smooth muscle relies primarily on heightened transport of extracellular calcium across the calcium membrane through receptor operated channels. The calcium channel (entry) blockers, verapamil, diltiazem and nifedipine inhibit noradrenalin induced elevations of calcium ion concentration in the vascular smooth muscle. They are completely absorbed after oral administration. Though all are effective vasodilators, nifedepine appears to be most potent in causing peripheral venous and arteriolar vasodilation[97].

Nifedipine reduces blood pressure and also induces reflex activation of sympathetic nervous system thereby increasing heart rate, cardiac output and myocardial contractility. Verapamil reduces systemic vascular resistance and causes moderate reduction in systemic arterial pressure. However it is contraindicated in congestive heart failure and in concomitant administration of beta-blockers. Diltiazem has most selective action on coronary vessels. Nifedipine can be combined with beta-blockers and in such a combination they have synergistic effect on blood pressure and block tachycardia[98].

Nifedipine is administered orally in a dose of 25 to 75 mg, however its effect is rapid when taken sublingually. The drug may be useful in selected patients with acute hypertension especially those with associated myocardial ischaemia. Facial flushing, headache, dizziness, nausea, vomiting and epigastric discomfort occur as side effects.

SELECTIVE ANTAGONISTS

Captopril

Captopril acts by inhibiting the enzyme (angiotensin converting enzyme, ACE) that converts inactive angiotensin I to an active pressor hormone angiotensin II. The sulphydryl group in the non-peptide captopril (D-3-mercapto-2-methyl propanoyl-L-proline) binds to the zinc present in the converting enzyme. Hence it appears to be of value in patients with severe hypertension having high plasma renin levels. Sometimes it is effective even in those with low plasma renin levels[99]. Probably it is due to its inhibitory action on enzyme kinase II that inactivates the vasodepressor hormone, bradykinin. Captopril has a dual action involving a decrease in the vasopressor hormone, angiotensin II and an increase in the vasodepressor hormone, bradykinin. It may also increase the level of another hormone, prostaglandin E producing vasodilatation[100]. There is fall in the level of renin and angiotensin I following administration of captopril.

Captopril is administered orally in a dose of 25 mg thrice daily. A smaller dose is desirable in those receiving diuretics or other antihypertensive agents. Great caution has to be taken in those with renal insufficiency as there is danger of occurrence of drug-induced renal failure[101], and also of nephrotic syndrome. Generally captopril is advocated in patients with relatively severe or refractory hypertension. However the response is unpredictable. Some respond very well and others fail to show any response.

Change in taste perception, skin rashes, proteinurea, leucopaenia and renal insufficiency may occur as side effects. During therapy with captopril, urine examination and leucocyte count should be done periodically.

Saralasin :

Saralasin (1-sar-8-ala-angiotensin II) is an angiotensin II peptide blocking agent. It produces a rapid fall in blood pressure in situations of hypertension associated with high renin state as encountered in a functionally significant unilateral renal artery stenosis. The drug is not effective in lowering blood pressure in patients with normal or low renin hypertension.

The administration of saralasin is associated with an increased plasma renin activity and a decrease in the level of aldosterone[102].

It is administered as rapid intravenous infusion in a dose of 10-20 microgram/kg/min. Salt restriction enhances its response. In majority of patients with 'angiotensinogenic hypertension' it produces a fall of more than 10 mm diastolic pressure within 1-2 minutes. As it can reduce blood pressure even when hypertension is not angiotensin mediated its use is limited only in patients who are salt depleted. The drug is of value as a rapid screening test to identify existence of surgically curable renal artery stenosis[27].

Though there are no known side effects, Saralasin can cause marked rise in blood pressure following discontinuation of saralasin infusion, and it may even cause an increased blood pressure during infusion in patients with low renin hypertension.

The pharmacologic action of diuretics, sympathetic depressants, beta-blockers and vasodilators is summarised in table VI.

Table VI : Action of antihypertensive agents

Type of drug	Peripheral vascular resistance	Plasma volume	Plasma renin activity	Cardiac output
Diuretics	↓	↓	↑	↔
Sympathetic depressants	↓	↑	↓	↔
Beta-blockers	↑	↔	↓	↓
Vasodilators	↓	↑	↑	↑

HYPERTENSION IN ELDERLY

In most populations the blood pressure tends to rise with advancing age[103]. The rise of systolic pressure is greater compared to that of the diastolic pressure. With advancing age the aorta and the peripheral arteries become increasingly rigid due to the loss of elasticity and deposition of calcium in the media. There is wide pulse pressure primarily due to high systolic blood pressure[104].

Aging is associated with decrease in cardiac output due to a fall in stroke volume. There is increase in peripheral vascular resistance. These changes are marked in those elderly exhibiting hypertension than in those with normotension. They are at an increased risk for development of cardiovascular complicantions and other target organ damange. There is decreased baroreceptor sensitivity with advancing age, and hypertension[105]. These situations bring about the alterations in baroreceptor sensitivity independently. There is failure of prompt compensatory vasoconstrictor reflexes to the changes in posture leading to postural hypotension. It is advisable to check blood pressure in the supine, the sitting and the standing positions in elderly. There is need for caution in administering adrenergic blocking drugs. The loss of autoregulation of cerebral blood flow enhances the adverse effects of adrenergic blocking drugs[106]. Drugs producing postural hypotension are dangerous.

The cerebral blood flow gets compromised in elderly exhibiting atherosclerosis and it may predispose to the occurrence of transient ischaemic attacks or cerebral thrombosis. The centrally acting anti-hypertensive agents are to be administered carefully. Beta-blockers are often selected in the treatment, as they do not adversely affect autoregulation of cerebral blood flow.

There is also progessive decrease in the renal blood flow and glomerular filtration rate. This process is aggravated in presence of hypertension, and hypertension predisposes to renal damage[107]. Renal concentrating ability gets reduced and renal conservation of sodium gets impaired during restricted intake of sodium[108]. This situation may increase the possibility of dehydration. Hence the diuretics are to be used with caution. There is also diminished renal tubular function causing defective tubular transport of salt, glucose and acid loads. Juxtaglomerular apparatus shows decreased activity leading to an alteration in renin-angiotensin-aldosterone response. With advancing age there is fall in plasma renin activity and plasma aldosterone level even in normotensive elders, and this fall is much more evident in elderly hypertensives.

These physiological alterations have created a need to undertake the treatment of hypertension in elderly with great caution. Generally treatment is undertaken with salt restriction and administration of thiazide and propranolol if necessary[109]. Hydralazine is a useful drug which often corrects postural hypotension in elderly.

The benefits of lowering blood pressure in mild hypertension remains uncertain. Hence there appears to be no need to initiate treatment in those with mild hypertension. As elderly patients exhibit adverse drug reactions, it is necessary to begin treatment with low doses and increase it gradually while carefully watching for adverse effects. The treatment must be undertaken in all elderly with moderate or severe hypertension because of high rate of cardiovascular complications. However caution has to be exercised in the treatment of patients with cerebrovascular or peripheral vascular diseases since decreased blood pressure may reduce tissue perfusion.

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HYPERTENSIVE CRISIS

A life threatening elevation of diastolic blood pressure (aboye 140 mm Hg) may develop in association with features of encephalopathy or with cerebral haemorrhage, subarachnoid haemorrhage, acute left ventricular failure, eclampsia, dissecting aortic aneurysm, acute myocardial infarction or pheochromocytoma. Such situations may also be encountered during cardiac catheterisation or after vascular reconstructive surgery or on sudden withdrawal of clonidine therapy. Hypertensive encephalopathy is associated with severe headache, nausea, vomiting, confusion, transient episodes of blurred vision, transient focal neurological deficits, convulsions or coma.

These clinical situations are not very common and are collectively referred as hypertensive crisis[110]. In such situations, the blood pressure has to be reduced to a level which relieves the immediate crisis. It is done as an emergency measure by administering rapidly acting intravenous drugs. Such a therapy is not indicated in situations associated with mere severe hypertension. Malignant hypertension is not considered similar to that of hypertensive encephalopathy. The former can exist in an asymptomatic person and may present without any neurological manifestations. These individuals require hospitalisation, evaluation and treatment with oral antihypertensive agents. Rapidly acting parenteral antihypertensive drugs show prompt action and bring an immediate control of blood pressure during acute phase of hypertensive crisis in a carefully monitored setting.

Sodium nitroprusside, diazoxide, trimethophan and phentolamine act immediately when administered intravenously and they have been shown very useful in the management of hypertensive crisis (table VII).

Table VII : Intravenous drugs with immediate action for hypertensive crisis

Drug	Dose	Mode of administration	Duration of action
Sodium nitroprusside	0.5 to 8 mcg/kg/min	infusion	1-5 min
Diazoxide	5 mg/kg	bolus	3-12 hours
Trimethophan	1– 10 mg/min	infusion	1-6 min
Phentolamine	1 –5 mg/min	bolus	15-60 min

Rapidly acting drugs have the advantage of their effect being controlled and easily reversed. Often one finds difficulty in distinguishing hypertensive encephalopathy from cerebrovascular accidents especially when the neurologic signs continue to persist. Reduction in blood pressure is followed by remarkable improvement in conditions of hypertensive encephalopathy.

Sodium Nitroprusside : Sodium nitroprusside is a powerful smooth muscle relaxant and it dilates both arterioles and venules. It lowers blood pressure instantaneously[111]. There is fall in the peripheral vascular resistance and reduction in venous return and cardiac output. There is no reflex tachycardia. The antihypertensive effect appears within minutes of administration of an adequate amount of nitroprusside. The action is short lived and the duration of action is for 1 to 5 minutes.

This drug frequently used for unloading the left ventricle has shown to be of value in hypertensive crisis. It is administered as continuous intravenous drip by dissolving 50 mg nitroprusside in 500 ml of 5% dextrose in water. The rate of flow is maintained initially at 20 micrograms/min and later it is slowly increased until the desired blood pressure is achieved. The dosage is to be controlled with an infusion pump. The drug is light sensitive and gets degraded into toxic thiocyanate; hence the infusion bottles are covered with dark coloured cloth or aluminium foil. Many patients require 50 to 200 micrograms/min. There is need to make measurements of blood pressure every 5 to 10 minutes during therapy.

The raised blood pressure should be lowered smoothly in small amounts ranging from 15 to 30 mm Hg of diastolic blood pressure so as to relieve the encephalopathy symptoms[112]. Then oral drugs are to be started and the parenteral therapy gradually discontinued. As thiocyanate may accumulate in blood on prolonged use or on large dose,particularly in presence of poor renal function, thiocyanate levels in the serum are to be monitored and its level should not exceed 10 mg/100 ml. Methaemoglobinaemia may be noted on prolonged use. Nausea, anorexia, skin rashes and headache may occur as side effects during its use.

Due to its rapid onset and offset of action, nitroprusside is useful in situations where rapid readjustments of blood pressure are needed. It is particularly advised in hypertensive crisis seen in severe left ventricular failure, and in patients with acute coronary or cerebrovascular insufficiency and pheochromocytoma. However this drug is used in places having intensive care facilities and continuous intra-arterial blood pressure monitoring.

Diazoxide : Diazoxide is a potent vasodilating agent and it lowers blood pressure for hours by causing arteriolar vasodilatation. It has a direct relaxant action on the smooth muscles of the arterioles. However the decrease in peripheral resistance is accompanied by reflex tachycardia, increased left ventricular contractility and cardiac output.

It should be used with great caution in patients with ischaemic heart disease. It should not be used in patients with dissecting aneurysm. As it does not affect the renal or cerebral blood flow it can be used safely in patients with renal or cerebrovascular disease. It is administered as a single intravenus bolus rapidly within 10 to 15 seconds period in a dose of 300 mg (5 mg/kg). The drug has to be administered rapidly to prevent neutralisation of its antihypertensive affect by serum protein binding[113]. Its antihypertensive action is noted in 1 to 2 minutes and it lasts for 3 to 12 hours. There is no need to administer the drug as continuous intravenous infusion. It can be administered twice or thrice in a 24-hours period. Unlike nitroprusside, diazoxide can be administered intermittently and it does not require continuous monitoring of pressure[114]. However the amount of fall in daistolic blood pressure is not definite and it may vary from 10 to 50 mm Hg.

Though diazoxide is chemically related to thiazide diuretics, paradoxically it causes pronounced sodium retention. Hence it is advisable to use diazoxide in combination with intravenous frusemide. Frusemide prevents sodium retention and potentiates the antihypertensive effect of diazoxide. Administration of multiple doses of diazoxide may be associated with hyperglycaemia due to inhibition of release of insulin.

Slow infusion of diazoxide appears to be as effective as bolus infusion. It has the advantage of not causing a precipitous fall of blood pressure.

Trimethophan : Trimethophan tosylate is a rapidly acting tertiary amine ganglion blocking agent. It inhibits sympathetic and parasympathetic outflow from the autonomic ganglia and causes reduction in blood pressure by relaxing both arteries and veins.

It is administered as an intravenous infusion in a dose of 1-10 mg/min and it has a rapid onset of action. The duration of action is brief lasting for 1-5 minutes. The effect is enhanced by keeping the patient in the head-up position. As it reduces the renal blood flow and glomerular filtration rate, trimethophan is avoided in patients with renal insufficiency. It is the drug of choice in the energetic treatment of dissecting asritic aneurysm as it decreases cardiac output by reducing left ventricular contraction velocity.

Trimethophan can't be used for prolonged period of time due to its parasympathetic side effects. Urinary retention, atony of the bowel and constipation occur as side effects. It is not advocated in post-operative situations.

Phentolamine : Phentolamine acts by blocking the action of circulating noradrenalin at alpha-adrenergic receptor sites. This alpha blockade is used in the treatment of hypertensive crisis from pheochromocytoma, clonidine withdrawal, and tyramine reactions., It may be given as bolus in a dose of 2-10 mg. Postural hypotension, weakness and impotency occur as side effects. It is contraindicated in severe coronary artery disease.

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REFERENCES

1. Pickering, G., : Hypertension. Amer. Jour. Med. 52: 570, 1972.
2. Shah, S. J., Pathak, Lekha, Shah, S., : Advances in patho-physiology and essential hypertension. Ind. Heart Jour. Teaching Series. No. 11, 519, 1981
3. World Health Organisation: Hypertension and coronary heart disease. Classification and critieria for epidemiological studies. Technical Report Series. No. 231, 1962.
4. Leading article: Catecholamines in essential hypertension. Lancet 1: 1088, 1977.
5. Page, I. H., : The nature of arterial hypertension. Arch. Intern. Med. 111: 106, 1963.
6. Borst, J.G.G., Borst de Geus, A., : Hypertension explained by Starling's theory of circulatory homoeotasis. Lancet 1: 677, 1963.
7. Ambard, L., Beaujard, E., : Causes de l' hypertension arteriellie. Arch. Gen. Med. 1: 520, 1904.
8. Dahl, L. K., Knudsen, K. D., Heine, M.A., et al : Effects of chronic excess salt ingestion. Circ. Res. 22: 11, 1968.
9. Oliver, W. J., Cohen, E. L., Keel, H.J.V., : Blood pressure, sodium intake and sodium related hormones in the Yanomamo Indians, a'no salt' culture. Circulation 52: 146, 1975.
10. Goldblatt, H., Lynch, J., Hanzal, R. B.: Studies in experimental hypertension: I. Production of persistent elevations of systemic blood pressure by means of renal ischaemia. Jour. Exp. Med. 59: 347, 1934.
11. Lucas, C., Ocoboch, R.W., Stern, M.P. et al : Disturbed relationship of plasma-renin to blood pressure in hypertension, Lancet 2: 1337, 1974.
12. Keeton, T. K., Campbell, W.B., : The pharmacologic alteration of renin release. Pharmacol. Rev. 31: 82, 1981.
13. Freeman, R. H., Davis, J. O., Johnson, J. A., et al: Arterial pressure regulation during hemorrhage: Homeostatic role of angiotension II. Proc. Soc. Exp. Biol. Med. 149: 19, 1975.
14. Gavras, H., Brunner, H. R., Vaughan, E. D., Jr., et al : Angiotensin-sodium interaction in blood pressure maintenance in renal hypertensive and normotensive rats. Science (Wash. D. C.) 1980: 1369, 1973.
15. Blair-West, J. R., Brook, A. H.,Gibson, A., et al: Effect of heptapeptide (2-8) and hexapeptide (3-8) fragments of angiotensin II on aldosterone secretion. Jour. Clino Endocrinol. 32: 575, 1971.
16. Stein,J. H., (ed): Internal Medicine, Boston, Little, Brown. 1983. p. 1961.
17. Laragh, J. H., : Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. Amer. Jour Med. 55: 211, 1973.
18. Taranzi, R. C., : Hemodynamic role of extracellular fluid in hypertension. Cir. Res. 38, Suppl. II: 73, 1976.
19. Carretero, O., Scicli, A. G.,: The renal kallikreinkinin system. Amer. Jour. Physiol 238: 247, 1980.

20. Zinner, S. H., Margolius, H. S., Rosner, B., et al: Stability of blood pressure reaction and urinary kallikrein concentration in childhood. An eight year follow-up. Circulation. 58: 908, 1978.

21. Lee, J. B., : Hypertension, natriurisis, and renomedullary prostaglandins. Amer. Rev. Prostaglandins. 3: 551, 1973.

22. Moncada, S., Vane, J. R., : Pharmacology and endogenous role of prostaglandin endoperoxidases, thromoboxane A2 and prostacyclin. Pharmacol. Rev. 30: 293, 1978.

23. Julius, S., Ester, M. D., Randall, O. S., : Role of autonomic nervous system in mild human hypertension. Cli. Science and Molecular Medicine, 48: 2435, 1975.

24. de Quattro, V,, Chan, S., : Raised plasma catecholamines in some patients with primary hypertension. Lancet 1: 806, 1972.

25. Chobanian, A. V., : Hypertension. Clinical symposia CIBA, 34: 3, 1982.

26. Ambsterdan, E. A., Couch, N. P., Christiliet, A. R., et al : Renal vein renin activity in the prognosis of renovascular hypertension. Amer. Jour. Med. 47. 860, 1969.

27. Steaten, D.H.P., Anderson, G. H., et al: Use of an angiotensin II antagonist (Saralasin) in the recognition of 'angiotensinogenic' hypertension. New Engl. Jour Med. 292: 657, 1975.

27. a. Madias, N. E., Millan V. G., : PTRA in the treatment of renovascular hypertension. Hosp. Prac. 16: 105, 1981.

28. Biglieri, E. G., et al : Adrenal mineralocorticoids causing hypertension. Amer. Jour. Med. 52: 623, 1972.

29. Davies, W. W., et al. : Bilateral adrenal hyperplasia as a cause of primary aldosteronism with hypertension, hyperkalemia and suppressed renin activity. Amer. Jour. Med. 42: 642, 1967.

29. a. Brown, J. J., Fraser, R., Love, D. R., et al : Apparently isolated excess deoxycorticosterone in hypertension. Lancet 2: 243, 1972.

30. Liddle, G. W., et al : A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. Trans. Ann. Am. Phys. 76: 199, 1963.

31. Engelman, K., : Pheochromocytoma. Clin. Endocrinol. Metab. 6: 769, 1977.

32. Beilin, L. J., Redman, C.W.G., Bonnar, J., In Hypertension: its nature and treatment. CIBA p. 99, 1974.

33. Leading article: Hypertension in pregnancy. Lancet 2: 487, 1975.

34. Spellacy, W. N., Birk, A. A., : The effect of intrauterine devices, oral contraceptives, oestrogens and progestogens on blood pressure. Amer. Jour. Obst. Gynecol. 112: 912, 1972.

35. Royal College of General Practitioners: Oral contraception study: Effect on hypertension and benign breast disease of progestagen component in combined oral contraceptives. Lancet. 1: 624, 1977.

36. Catt, K. J., Cain, M. D., Menard, J., : Radioimmunoassay study of the renin-angiotensin system in human hypertension and during oestrogen treatment, In Hypertension, New York, Springer-Verlag, p. 591, 1972.

37. Davies, G. J., Rhodes, J., Calcraft, B. J., : Complications of carbenoxolone therapy. Brit. Med. Jour 3: 400, 1974.

38. McFiff, J. C. Crowshaw, K., Terragno, N. K., et al : Prostaglandin-like substances appearing in canine renal blood during renal ischemia : Their partial characterization by pharmacologic and chromatographic procedures. Circ. Res. 27: 765, 1970.

39. Kannel, W. B., Sorlie, P., : Hypertension in Framingham. in Paul, O., (ed) Epidemiology and control of hypertension. Miami Symposia specialists, p 553, 1975.

40. Hamer, J., : Modern management of hypertension. in Hamer, J., Rowlands, D. J. (ed) Recent advances in cardiology Edinburgh, Churchill Livingstone, p 1, 1981.

41. Veterans Administration cooperative study group on antihypertensive agents: Effects of treatment on morbidity in hypertension : Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Jour. Amer. Med. Assn. 202: 1028, 1967.

42. Idem: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. ibid. 213: 1143, 1970.

43. Hypertension detection and follow-up program cooperative group. Five year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure,including mild hypertension. Jour. Amer. Med. Assn. 242: 2562, 1979.

44. The Australian therapeutic trial in mild hypertension: Report by the management committee, Lancet, 1: 1261, 1980.

45. Heigeland, A., : Treatment of mild hypertension: a five year controlled drug trial : the Oslo Study. Amer. Jour. Med. 69: 653, 1980.

46. Multiple risk factor intervention trial research group: risk factor changes and mortality results. Jour. Amer. Med. Assn. 248: 1465, 1982.

47. Freis, E. D., : Mild hypertension, which patients to treat. Postgrad. Med. 73: 180, 1983.

48. Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch. Intern. Med. 140: 1280, 1980.

49. Shapiro, A. P., : Hypertension -- Current Management,Part II. DM — Disease-a-Month, 23: 3, 1977.

49. a. Finnerty, F. A. Jr., : Step-down therapy in hypertension : importance in long-term management. Jour. Amer. Med. Assn. 246: 2593, 1981.

50. Laragh, J. H., : Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. Amer. Jour. Med. 55: 261, 1973.

51. Messerli, F. H., : Individualization of antihypertensive therapy : an approach based on hemodynamics and age. Jour. Clin. Pharmacol. 21: 517, 1981.

52. Kaplan, N. M., : New approaches to the therapy of mild hypertension. Amer. Jour. Cardiol. 51: 621, 1983.

53. Okun, R., : Effectiveness of prazosin as initial antihypertensive therapy. Amer. Jour. Cardiol. 51: 644, 1983.
54. Buhler, F. R., Burkart, F., Lutold, B.E., et al: Antihypertensive beta blocking action as related to renin and age: a pharmacologic tool to identify pathogenic mechanisms in essential hypertension. Amer. Jour. Cardiol. 36: 653, 1975.
55. Cutler, R., in Round table discussion— Initial therapy in hypertension. Amer. Jour. Cardiol. 51: 657, 1983.
56. Dahl, L. K., Leitl, G., Heine, M.,: Influence of dietary potassium and sodium. Potassium molar ratios on the dietary development of salt hypertension. Jour. Exp. Med. 136. 318, 1972.
57. Chaing, B. N. Perlman, I. V., Epstein, F. H., : Overweight and hypertension. Circulation. 39: 403, 1969.
58. Ramsay, L. E., Ramsay, M. H., Hettiarachchi, J., et al: Weight reduction in blood pressure clinic. Brit. Med. Jour. 2: 244, 1977.
59. Patel, C., : 12-month follow-up of yoga and biofeedback in the management of hypertension. Lancet 1: 62, 1975.
60. Wallace, R. K., : Physiological effects of transcendental meditation. Science. 167: 1751, 1970.
61. Frenkel, B. L., Patel, D. J., Horwitz, D., et al: Treatment of hypertension with biofeedback and relaxation techniques. Psychosom. Med. 40: 276, 1978.
62. Cranston, W. I., Juel-Jensen, B.E., Semmence, A. M., et al: Effects of oral diurectics on raised arterial pressure. Lancet 2: 966, 1963.
63. McLeod, P. J., Ogilvie, R. I., Ruedy, J., : Effects of large and small doses of hydrochlorothiazide in hypertensive patients. Clin. Pharm. Exp. Ther. 11: 733, 1970.
64. Bennett, W. M., Porter, G. A., : Efficiency and safety of metolazone in renal failure and nephrotic syndrome. Jour. Clin. Pharmacol. 13: 357, 1973.
65. Weber, J. C. P., Bird, H., Cosh, J., et al : Once-daily treatment of mild to moderate hypertension with xipamide:a controlled study. Brit. Jour. Clin. Pharmacol. 4: 283, 1977.
66. Turner, P. Volans, G. N. Rogers, H. T.,: Initial controlled evaluation of antihypertensive drug: a study with indapamide. Current Medical Research Opinion 5: supplement 1: 124, 1977.
67. Ames, R. P., : Negative effects of diuretic drugs on metabolic risk factors for coronary heart disease; possible alternative drug therapies. Amer. Jour. Cardiol. 51: 632, 1983.
68. Tarazi, R. C., Gifford, R. W., : Drug treatment of hypertension. Current Cardiovascular Topics, Vol. 1, Part 2 in Drugs in Cardiology, ed. Donoso, E., Stuttgart, George Thieme, 1975.
69. Anderson, J., Godfrey, B. E., Hill, D. M., et al : A comparison of the effects of hydrochlorothiazide and frusemide in the treatment of hypertensive patients. Quart. Jour. Med. 160: 541, 1974.
70. Henning, M., : Studies on the mode of action alpha methyldopa. Acta Physiol. Scand (Suppl) 32: 1, 1969.

71. Johnston, P., Kitchin, A. H., Lowther, C. P., : Treatment of hypertension with methyl dopa. Brit. Med. Jour. **1:** 133, 1966.

72. Haeusler, G., : Cardiovascular regulation by central adrenergic mechanisms and its alteration by hypotensive drugs. Circulation Research 36 Suppl. **I,** 233, 1975.

73. Hunyor, S. N., Hansson. L., Harrison, T. S. et al., : Effects of clonidine withdrawal. Possible mechanisms and suggestions for management. Brit. Med. Jour. **2:** 209, 1973.

74. Bein, H. J.,: The pharmacology of Rauwolfia. Pharmacol. Rev. **8:** 435, 1956.

751. Armstrong, B., Stevens, N., Doll, R., : Retrospective study of the association between the use of Rauwolfia derivatives and breast cancer in English women. Lancet. **2:** 672, 1974.

76. Golderg, A. D. Raftery, E. B., : Patterns of blood pressure during chronic administration of a postaganglionic sympathetic blocking drugs for hypertension. Lancet. **2:** 1052, 1976.

77. Frohlich, E. D., : Inhibition of adrenergic function in the treatment of hypertension. Arch. Intern. Med. **133:** 1033, 1974.

78. Shen, D., Gibaldi, M. Throne, M., et al: Pharmacokinetics of bethanidine in hypersensitive patients. Clin. Pharmacol. Ther. **17:** 363, 1975.

79. Orgain, E. S. Kern, A., : Debrisoquin in the therapy of hypertension. Arch. Intern. Med. **125:** 255, 1970.

80. Simpson, F. O., : Beta-adrenergic blocking drugs in hypertension. Drugs. **85-105:** 1974.

81. Fitzerald, J. D., : Beta adrenergic blocking drugs: Present position and future developments. Acta Cardiologica, Suppl. **15,** 199: 1972.

82. Prichard, B. N. C., : The place of beta adrenoceptor blocking drugs in the treatment of hypertension, In Clinical Hypertension, Shah, N. J., Singhvi, P(ed) Bombay, Meducation Service, 1979, p. 46.

84. Hampton, J. R., : Should every survivor of a heart attack be given a beta-blocker? Brit. Med. Jour. **285:** 33, 1982.

85. Day, J. L., Metcalfe, J., Simpson, C. N., : Adrenergic mechanisms in control of plasma lipid concentrations. Brit. Med. Jour. **284:** 1145, 1982.

86. Lund-Johnsen, P., : Hemodynamic consequences of long-term beta-blocker therapy: a 5-year follow-up study of atenolol. Jour. Cardiovas. Pharmacol. **1:** 487, 1979.

87. Richards, D. A., . Pharmacological effects of labetalol in man. Brit. Jour. Clin. Pharm. **3:** 721, 1976.

88. Stokes, G. S. Frost, G. W., Graham, R. M., et al : Indoramin and prazosin as adjuncts to beta-adrenoceptor blockade in hypertension. Clin. Pharm. Ther. **24:** 783, 1979.

89. Khatri, B., Uemura, N., Notargiacomo., a., et al; Direct and reflex cardiostimulatory effect of hydralazine. Amer. Jour. Cardiol. **49:** 38, 1977.

90. O'Malley, K., Segal, J. L., Israili, Z. H., et al: Duration of of hydralazine action in hypertension. Clin. Pharm. Exptl Therapeutics. **18:** 581, 1975.

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91. Pettinger, W., Mitchell, H. C., : Minoxidil - an alternative to nephrectomy for refractory hypertension. New Engl. Jour. Med. 289: 167, 1973.

92. Wilburn, R. L., Blaufuss, A., : Long-term treatment of severe hypertension with minoxidil, propranolol and furosemide. Circulation, 52: 706, 1975.

93. Graham, R. M. Pettinger, W. A., Prazosin, New Engl. Jour. Med. 300: 232, 1979.

94. Lowenstein, J., Steele, N. M., : Prazosin. Amer. Heart Jour. 95: 262, 1978.

95. Cutler, R., : Effect of antihypertensive agents on lipid metabolism. Amer. Jour Cardiol. 51: 628, 1983.

96. Stokes, G. S., Graham, R. M., Gain, J. M., et al : Influence of dosage and dietary sodium on the first-dose effects of prazosin. Brit. Med. Jour. 1: 1507, 1977.

97. Zelis, R. F., : Calcium entry blockers in cardiologic therapy. Hosp. Pract. 16: 49, 1981.

98. Aoki, K., Kondo, S., Mochizuki, A., et al., : Antihypertensive effect of cardiovascular $Ca2 +$ —antagonist in hypertensive patients in the absence of and presence of beta-adrenergic blockers. Amer. Heart Jour. 96: 218, 1978.

99. Gavras, H., Brummer, H. R., Turini, G. A., et al : Antihypertensive effect of oral angiotensin converting enzyme inhibitor SQ 14225. New Engl. Jour. Med. 298: 991, 1978.

100. Kaplan, N. M., : Newer antihypertensive agents. When to try them. Postgrad. Med. 73: 213, 1983.

101. Farrow, P. R., Wilkinson, R., : Reversible renal failure during treatment with captopril. Brit. Med. Jour. 1: 1680, 1979.

102. Baker, K. M., Johns, D. W., Vaughan, E. D. Jr., et al : Antihypertensive effects of angiotensin blockade. Saralasin versus captopril. Clin. Exp. Hypertension 2: 947, 1980.

103. Amery, A., Wasir, H., Bulpitt, C., et al : Aging and the cardiovascular system. Acta Cardiol (Brux) 6: 443, 1978.

104. Lowenthal, D. T., Kim., K. E., Affrime, M. B., et al., : Overview of physiology of senescence. Chest suppl. 2: 408, 1983.

105. Bristow, J. D., Honour, A. J.. Pickering, G. W., et al : Diminished baorefle sensitivity in high blood pressure. Circulation 39: 48, 1969.

106. Woolner, L., McCarthy, S. T., Soper, N. D. W., et al : Failure of cerebral autoregulation as a cause of brain dysfunction in elderly. Brit. Med. Jour. 1: 1117, 1979.

107. Moyer, J. H., Heider, C. T., Pevery, K., et al., : The vascular status of heterogeneous group of patients with hypertension with particular emphasis on renal function. Amer. Jour. Med. 24: 164, 1958.

108. Epstein, M., Hollenberg, N. K., : Age as determinant of renal sodium conservation in normal man. Jour. Lab. Clin. Med. 87: 411, 1976.

109. Morgan, T., Adam, W., Gillies, a., et al : Treatment of mild hypertension. Clin. Science and Molecular Medicine. 55: 305, 1978.

110. Sheps, S. G., : Hypertensive crisis. Postgrad. Med. 49, 95, 1971.
111. Tuzel, I., Limijuco, R., Kahn, D., : Sodium nitroprusside in hypertensive crisis. Curr. Ther. Res. 17: 95, 1975.
112. Palmer, R. F., Lasseter, K. C., : Use and toxicity of nitroprusside, 292; 1081, 1975.
113. Sellers, E. M., Koch-Weser. J., : Influence of intravenous injection rate on protein binding and vascular activity of diazoxide. Ann. N. Y. Acad. Sci. 226: 319, 1973.
114. Thien, T. A., Huysmens, P. J. M., Gerlag, P.G.G. et al : Diazoxide infusion in severe hypertension and hypotension. Clin. Pharm. Therap. 25: 795, 1979.

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